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(54) Title: NOVEL GENES, COMPOSITIONS, KITS, AND METHODS FOR IDENTIFICATION, ASSESSMENT, PREVENTION, AND THERAPY OF CERVICAL CANCER

(57) Abstract: The invention relates to newly discovered nucleic acid molecules and proteins associated with cervical cancer including pre-malignant conditions such as dysplasia. Compositions, kits, and methods for detecting, characterizing, preventing, and treating human cervical cancers are provided.



WO 02/101075 A2

NOVEL GENES, COMPOSITIONS, KITS, AND METHODS FOR
IDENTIFICATION, ASSESSMENT, PREVENTION, AND THERAPY OF
CERVICAL CANCER

5 RELATED APPLICATIONS

The present application claims priority to U.S. provisional patent application serial no. 60/298,159, filed on June 13, 2001, U.S. provisional patent application serial no. 60/298,155, filed on June 13, 2001, and U.S. provisional patent application serial no. 60/335,936, filed on November 14, 2001, all of which are expressly incorporated by
10 reference.

FIELD OF THE INVENTION

The field of the invention is cervical cancer, including diagnosis, characterization, management, and therapy of cervical cancer.

15

BACKGROUND OF THE INVENTION

The increased number of cancer cases reported in the United States, and, indeed, around the world, is a major concern. Currently there are only a handful of treatments available for specific types of cancer, and these provide no absolute guarantee
20 of success. In order to be most effective, these treatments require not only an early detection of the malignancy, but a reliable assessment of the severity of the malignancy.

Cancer of the cervix is one of the most common malignancies in women and remains a significant public health problem throughout the world. In the United States alone, invasive cervical cancer accounts for approximately 19% of all
25 gynecological cancers. In 1996, it was estimated that there were 14,700 newly diagnosed cases and 4900 deaths attributed to this disease (American Cancer Society, Cancer Facts & Figures 1996, Atlanta, Ga.: American Cancer Society, 1996). In many developing countries, where mass screening programs are not widely available, the clinical problem is more serious. Worldwide, the number of new cases is estimated to be 471,000 with a
30 four-year survival rate of only 40% (Munoz et al., 1989, *Epidemiology of Cervical Cancer* In: "Human Papillomavirus", New York, Oxford Press, pp 9-39; National Institutes of Health, Consensus Development Conference Statement on Cervical Cancer, Apr.1-3, 1996).

The precursor to cervical cancer is dysplasia, also known in the art as cervical intraepithelial neoplasia (CIN) or squamous intraepithelial lesions (SIL). While it is not understood how normal cells become transformed, the concept of a continuous spectrum of histopathological change from normal, stratified epithelium through CIN to
5 invasive cancer has been widely accepted for many years. A large body of epidemiological and molecular biological evidence has established human papillomavirus (HPV) infection as a causative factor in cervical cancer. HPV is found in 85% or more of squamous cell invasive lesions, which represent the most common histologic type seen in cervical carcinoma. Additional cofactors have also been
10 identified, including oncogenes that have been activated by point mutations and chromosomal translocations or deletions.

In light of this, cervical cancer remains a highly preventable form of cancer when pre-invasive lesions are detected early. Cytological examination of Papanicolaou-stained cervical smears (also referred to as Pap smears) is currently the
15 principle method for detecting cervical cancer. Not surprisingly, the effectiveness of Pap smear screening varies depending not only upon the quality of the sample being used, but also upon subjective parameters that are inherent to the analysis. In addition, despite the historical success of the test, concerns have arisen regarding its ability to reliably predict the behavior of some pre-invasive lesions (Ostor *et al.*, 1993, *Int. J. Gynecol.*
20 *Pathol.* 12: 186-192; and Genest *et al.*, 1993, *Human Pathol.* 24: 730-736).

SUMMARY OF THE INVENTION

The invention relates to cancer markers (hereinafter “markers” or “markers of the inventions”), which are listed in Table 1. The invention provides
25 nucleic acids and proteins that are encoded by or correspond to the markers (hereinafter “marker nucleic acids” and “marker proteins,” respectively). Table 1 provides the sequence identifiers of the sequences of such marker nucleic acids and proteins listed in the accompanying Sequence Listing. The invention further provides antibodies, antibody derivatives and antibody fragments which bind specifically with such proteins
30 and/or fragments of the proteins.

The invention also relates to various methods, reagents and kits for diagnosing, staging, prognosing, monitoring and treating cervical cancer. “Cervical cancer “ as used herein includes carcinomas, (*e.g.*, carcinoma in situ, invasive

carcinoma, metastatic carcinoma) and pre-malignant conditions, (*e.g.*, dysplasia, including CIN or SIL). In one embodiment, the invention provides a diagnostic method of assessing whether a patient has cervical cancer or has higher than normal risk for developing cervical cancer, comprising the steps of comparing the level of expression of
5 a marker of the invention in a patient sample and the normal level of expression of the marker in a control, *e.g.*, a sample from a patient without cervical cancer. A significantly higher level of expression of the marker in the patient sample as compared to the normal level is an indication that the patient is afflicted with cervical cancer or has higher than normal risk for developing cervical cancer.

10 According to the invention, the markers are selected such that the positive predictive value of the methods of the invention is at least about 10%, preferably about 25%, more preferably about 50% and most preferably about 90%. Also preferred for use in the methods of the invention are markers that are differentially expressed, as compared to normal cervical cells, by at least two-fold in at least about 20%, more
15 preferably about 50% and most preferably about 75% of any of the following conditions: stage 0 cervical cancer patients, stage I cervical cancer patients, stage II cervical cancer patients, stage III cervical cancer patients, stage IV cervical cancer patients, grade I cervical cancer patients, grade II cervical cancer patients, grade III cervical cancer patients, squamous cell (epidermoid) cervical cancer patients, cervical adenocarcinoma
20 patients, cervical adenosquamous carcinoma patients, small-cell cervical carcinoma patients, malignant cervical cancer patients, patients with primary carcinomas of the cervix, patients with primary malignant lymphomas of the cervix and patients with secondary malignant lymphomas of the cervix, and all other types of cancers, malignancies and transformations associated with the cervix.

25 In a preferred diagnostic method of assessing whether a patient is afflicted with cervical cancer (*e.g.*, new detection ("screening"), detection of recurrence, reflex testing), the method comprises comparing:

- a) the level of expression of a marker of the invention in a patient sample, and
- 30 b) the normal level of expression of the marker in a control non-cervical cancer sample.

A significantly higher level of expression of the marker in the patient sample as compared to the normal level is an indication that the patient is afflicted with cervical cancer.

The invention also provides diagnostic methods for assessing the efficacy
5 of a therapy for inhibiting cervical cancer in a patient. Such methods comprise comparing:

- a) expression of a marker of the invention in a first sample obtained from the patient prior to providing at least a portion of the therapy to the patient, and
- 10 b) expression of the marker in a second sample obtained from the patient following provision of the portion of the therapy.

A significantly lower level of expression of the marker in the second sample relative to that in the first sample is an indication that the therapy is efficacious for inhibiting cervical cancer in the patient.

15 It will be appreciated that in these methods the “therapy” may be any therapy for treating cervical cancer including, but not limited to, chemotherapy, radiation therapy, surgical removal of tumor tissue, gene therapy and biologic therapy such as the administering of antibodies and chemokines. Thus, the methods of the invention may be used to evaluate a patient before, during and after therapy, for
20 example, to evaluate the reduction in tumor burden.

In a preferred embodiment, the diagnostic methods are directed to therapy using a chemical or biologic agent. These methods comprise comparing:

- a) expression of a marker of the invention in a first sample obtained from the patient and maintained in the presence of the chemical or biologic
25 agent, and
- b) expression of the marker in a second sample obtained from the patient and maintained in the absence of the agent.

A significantly lower level of expression of the marker in the second sample relative to that in the first sample is an indication that the agent is efficacious for inhibiting cervical
30 cancer, in the patient. In one embodiment, the first and second samples can be portions of a single sample obtained from the patient or portions of pooled samples obtained from the patient.

The invention additionally provides a monitoring method for assessing the progression of cervical cancer in a patient, the method comprising:

- a) detecting in a patient sample at a first time point, the expression of a marker of the invention;
- 5 b) repeating step a) at a subsequent time point in time; and
- c) comparing the level of expression detected in steps a) and b), and therefrom monitoring the progression of cervical cancer in the patient.

A significantly higher level of expression of the marker in the sample at the subsequent time point from that of the sample at the first time point is an indication that the cervical
10 cancer has progressed, whereas a significantly lower level of expression is an indication that the cervical cancer has regressed.

The invention further provides a diagnostic method for determining whether cervical cancer has metastasized or is likely to metastasize in the future, the method comprising comparing:

- 15 a) the level of expression of a marker of the invention in a patient sample, and
- b) the normal level (or non-metastatic level) of expression of the marker in a control sample.

A significantly higher level of expression in the patient sample as compared to the
20 normal level (or non-metastatic level) is an indication that the cervical cancer has metastasized or is likely to metastasize in the future.

The invention moreover provides a test method for selecting a composition for inhibiting cervical cancer in a patient. This method comprises the steps of:

- 25 a) obtaining a sample comprising cancer cells from the patient;
- b) separately maintaining aliquots of the sample in the presence of a plurality of test compositions;
- c) comparing expression of a marker of the invention in each of the aliquots; and
- 30 d) selecting one of the test compositions which significantly reduces the level of expression of the marker in the aliquot containing that test composition, relative to the levels of expression of the marker in the presence of the other test compositions.

The invention additionally provides a test method of assessing the cervical carcinogenic potential of a compound. This method comprises the steps of:

- a) maintaining separate aliquots of cervical cells in the presence and absence of the compound; and
- 5 b) comparing expression of a marker of the invention in each of the aliquots.

A significantly higher level of expression of the marker in the aliquot maintained in the presence of the compound, relative to that of the aliquot maintained in the absence of the compound, is an indication that the compound possesses cervical carcinogenic potential.

10 In addition, the invention further provides a method of inhibiting cervical cancer in a patient. This method comprises the steps of:

- a) obtaining a sample comprising cancer cells from the patient;
- b) separately maintaining aliquots of the sample in the presence of a plurality of compositions;
- 15 c) comparing expression of a marker of the invention in each of the aliquots; and
- d) administering to the patient at least one of the compositions which significantly lowers the level of expression of the marker in the aliquot containing that composition, relative to the levels of expression of the marker in the presence of the other compositions.

20 In the aforementioned methods, the samples or patient samples comprise cells obtained from the patient. The cells may be found in a cervical smear collected, for example, by a cervical brush. In another embodiment, the sample is a body fluid. Such fluids include, for example, blood fluids, lymph, ascitic fluids, gynecological fluids, urine, and fluids collected by vaginal rinsing. In a further embodiment, the patient sample is *in vivo*.

According to the invention, the level of expression of a marker of the invention in a sample can be assessed, for example, by detecting the presence in the sample of:

- 30 • the corresponding marker protein (*e.g.*, a protein having one of the sequences set forth as “SEQ ID NO (AAs)” in Table 1, or a fragment of the protein (*e.g.* by using a reagent, such as an antibody, an antibody derivative,

an antibody fragment or single-chain antibody, which binds specifically with the protein or protein fragment)

- the corresponding marker nucleic acid (*e.g.* a nucleotide transcript having one of the nucleic acid sequences set forth as “SEQ ID NO (nts)” in Table 1, or a complement thereof), or a fragment of the nucleic acid (*e.g.* by contacting transcribed polynucleotides obtained from the sample with a substrate having affixed thereto one or more nucleic acids having the entire or a segment of the nucleic acid sequence of any of the SEQ ID NO (nts), or a complement thereof)
- a metabolite which is produced directly (*i.e.*, catalyzed) or indirectly by the corresponding marker protein.

According to the invention, any of the aforementioned methods may be performed using a plurality (*e.g.* 2, 3, 5, or 10 or more) of cervical cancer markers, including cervical cancer markers known in the art. In such methods, the level of expression in the sample of each of a plurality of markers, at least one of which is a marker of the invention, is compared with the normal level of expression of each of the plurality of markers in samples of the same type obtained from control humans not afflicted with cervical cancer. A significantly altered (*i.e.*, increased or decreased as specified in the above-described methods using a single marker) level of expression in the sample of one or more markers of the invention, or some combination thereof, relative to that marker's corresponding normal or control level, is an indication that the patient is afflicted with cervical cancer. For all of the aforementioned methods, the marker(s) are preferably selected such that the positive predictive value of the method is at least about 10%.

In a further aspect, the invention provides an antibody, an antibody derivative, or an antibody fragment, which binds specifically with a marker protein (*e.g.*, a protein having one of the amino acid sequences set forth in the Sequence Listing) or a fragment of the protein. The invention also provides methods for making such antibody, antibody derivative, and antibody fragment. Such methods may comprise immunizing a mammal with a protein or peptide comprising the entirety, or a segment of 10 or more amino acids, of a marker protein (*e.g.*, a protein having one of the amino acid sequences set forth in the Sequence Listing), wherein the protein or peptide may be obtained from a cell or by chemical synthesis. The methods of the invention also encompass producing

monoclonal and single-chain antibodies, which would further comprise isolating splenocytes from the immunized mammal, fusing the isolated splenocytes with an immortalized cell line to form hybridomas, and screening individual hybridomas for those that produce an antibody that binds specifically with a marker protein or a
5 fragment of the protein.

In another aspect, the invention relates to various diagnostic and test kits. In one embodiment, the invention provides a kit for assessing whether a patient is afflicted with cervical cancer. The kit comprises a reagent for assessing expression of a marker of the invention. In another embodiment, the invention provides a kit for
10 assessing the suitability of a chemical or biologic agent for inhibiting cervical cancer in a patient. Such a kit comprises a reagent for assessing expression of a marker of the invention, and may also comprise one or more of such agents. In a further embodiment, the invention provides kits for assessing the presence of cervical cancer cells or treating cervical cancers. Such kits comprise an antibody, an antibody derivative, or an antibody
15 fragment, which binds specifically with a marker protein, or a fragment of the protein. Such kits may also comprise a plurality of antibodies, antibody derivatives, or antibody fragments wherein the plurality of such antibody agents binds specifically with a marker protein, or a fragment of the protein.

In an additional embodiment, the invention also provides a kit for
20 assessing the presence of cervical cancer cells, wherein the kit comprises a nucleic acid probe that binds specifically with a marker nucleic acid or a fragment of the nucleic acid. The kit may also comprise a plurality of probes, wherein each of the probes binds specifically with a marker nucleic acid, or a fragment of the nucleic acid.

In a further aspect, the invention relates to methods for treating a patient
25 afflicted with cervical cancer or at risk of developing cervical cancer. Such methods may comprise reducing the expression and/or interfering with the biological function of a marker of the invention. In one embodiment, the method comprises providing to the patient an antisense oligonucleotide or polynucleotide complementary to a marker nucleic acid, or a segment thereof. For example, an antisense polynucleotide may be
30 provided to the patient through the delivery of a vector that expresses an anti-sense polynucleotide of a marker nucleic acid or a fragment thereof. In another embodiment, the method comprises providing to the patient an antibody, an antibody derivative, or antibody fragment, which binds specifically with a marker protein or a fragment of the

protein. In a preferred embodiment, the antibody, antibody derivative or antibody fragment binds specifically with a protein having one of the amino acid sequences set forth in the Sequence Listing, or a fragment of the protein.

It will be appreciated that the methods and kits of the present invention
5 may also include known cancer markers including known cervical cancer markers. It will further be appreciated that the methods and kits may be used to identify cancers other than cervical cancer.

DETAILED DESCRIPTION OF THE INVENTION

10 The invention relates to newly discovered cancer markers associated with the cancerous state of cervical cells. It has been discovered that the higher than normal level of expression of any of these markers or combination of these markers correlates with the presence of cervical cancer including pre-malignant conditions such as dysplasia, in a patient. Methods are provided for detecting the presence of cervical
15 cancer in a sample, the absence of cervical cancer in a sample, the stage of a cervical cancer, and other characteristics of cervical cancer that are relevant to prevention, diagnosis, characterization, and therapy of cervical cancer in a patient. Methods of treating cervical cancer are also provided.

Table 1 lists the markers of the invention which are over-expressed in
20 cervical cancer cells compared to normal (*i.e.*, non-cancerous) cervical cells and comprises markers listed in Tables 2 and 3. Table 2 lists newly-identified nucleotide and amino acid sequences. Table 3 lists newly-identified nucleotide sequences. Tables 1-3 provide the sequence listing identifiers of the cDNA sequence of a nucleotide transcript and the amino acid sequence of a protein encoded by or corresponding to each
25 marker, as well as the location of the protein coding sequence within the cDNA sequence.

Table 1

Marker	Gene Name	SEQ ID NO (nts)	SEQ ID NO (AAs)	CDS
M661	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 1	1	2	223..11946
M662	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 2	3	4	223..11922
M663	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 3	5	6	223..12000
M664	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 4	7	8	223..11976
M1	APOL1: Apolipoprotein L-I mRNA, splice variant A, major form	9	10	213..1364
M2	APOL1: Apolipoprotein L-I mRNA, splice variant B, minor form	11	12	274..1518
M3	APOL3: apolipoprotein L, 3; TNF-inducible protein CG12-1	13	14	418..1413
OV3	AQP5: Aquaporin 5	15	16	519..1316
M4	BC001980: clone MGC:5618	17	18	157..225
M5	BST2: Bone marrow stromal cell antigen 2	19	20	10..552
M6	BTEB1: basic transcription element binding protein 1	21	22	1265..1999
M665	CD74: CD74 antigen (invariant polypeptide of major histocompatibility complex, class II antigen-associated)	23	24	8..706
M7	CDC20: CDC20 cell cycle protein	25	26	45..1544
M8	CDKN2C: cyclin-dependent kinase inhibitor 2C, p18	27	28	1216..1722
M9	CKTSF1B1: (cysteine knot superfamily 1, BMP antagonist 1), gremlin	29	30	45..1544
M10	CLDN1: claudin 1	31	32	221..856
M11	CLIC4: chloride intracellular channel 4	33	34	198..959
M12	COL1A1: collagen, type I, alpha 1	35	36	120..4514
M13	COL1A2: collagen, type I, alpha 2	37	38	140..4240
M14	COL8A1: collagen, type VIII, alpha 1	39	40	1..2235
M15	COPA: coatamer protein complex, subunit alpha	41	42	467..4141
M16	CRIP1: cysteine-rich protein 1 (intestinal)	43	44	1..234
M17	CTGF: connective tissue growth factor	45	46	146..1195
M18	DOC: downregulated in ovarian cancer 1	47	48	135..2393
M19	EFNA1: ephrin-A1	49	50	74..691
M481	EPPK1: epiplakin 1	51	52	89..15286
M20	FLJ11350: hypothetical protein FLJ11350	53	54	106..1047
M21	FLJ13809: hypothetical protein FLJ13809	55	56	64..1593
M22	FLJ20500: hypothetical protein FLJ20500	57	58	198..896
M23	FLJ23399: hypothetical protein FLJ23399	59	60	283..1770
M24	FN1: Fibronectin 1, variant 1	61	62	<1..2384
M25	FN1: Fibronectin 1, variant 2	63	64	<1..6988
M482	FOSL2: FOS-like antigen 2, variant 1	65	66	324..1304
M483	FOSL2: FOS-like antigen 2, variant 2	67	66	324..1304
M484	FSHPRH1: FSH primary response (LRPR1, rat) homolog 1	68	69	270..2540
M26	FY: Duffy blood group	70	71	495..1511

M485	G1P3:interferon, alpha-inducible protein (clone IFI-6-16)	72	73	108..500
M486	GW112: GW112 protein	74	75	509..1072
M27	HSKERUV: clone 266, Human radiated keratinocyte mRNA 266 (keratin-related protein)	76	77	<1..801
M28	HSPC121: butyrate-induced transcript 1	78	79	150..1271
M29	HUMCLPB: Coactosin like protein	80	81	150..576
M487	hypothetical protein	82	83	58..8163
M30	IFI27: (interferon, alpha-inducible protein 27	84	85	55..423
OV31	IFI30: interferon, gamma-inducible protein 30	86	87	41..952
M31	IFITM2: interferon induced transmembrane protein 2 (1-8D)	88	89	280..678
M32	IGFBP-3: insulin-like growth factor binding protein 3	90	91	133..1009
M33	IL8RA: interleukin 8	92	93	75..374
M34	INHBA: Inhibin, beta-1	94	95	86..1366
M488	ITGA3: integrin, alpha 3 (antigen CD49C, alpha 3 subunit of VLA-3 receptor), variant a	96	97	74..3229
M454	ITGA3: integrin, alpha 3 (antigen CD49C, alpha 3 subunit of VLA-3 receptor), variant b	98	99	74..3274
M35	ITGB6: integrin, beta 6	100	101	195..2561
M36	KATII: L-kynurenine/alpha-aminoadipate aminotransferase	102	103	454..1731
M666	KCNAB1: potassium voltage-gated channel, shaker-related subfamily, beta member 1, variant 1	104	105	89..1315
M667	KCNAB1: potassium voltage-gated channel, shaker-related subfamily, beta member 1, variant 2	106	107	54..1313
M668	KCNAB1: potassium voltage-gated channel, shaker-related subfamily, beta member 1, variant 3	108	109	28..1233
M37	KIAA0662: KIAA0662 protein	110	111	<1..2035
M38	LAMA3: Laminin, alpha-3 (nicein (150kD), (kalinin (165kD), BM600 (150kD)	112	113	1..5142
M39	LAMC2: laminin, gamma 2	114	115	90..3671
M40	LSM5: U6 snRNA-associated Sm-like protein	116	117	1..276
M41	LUM: lumican	118	119	85..1101
M42	MACMARCKS: macrophage myristoylated alanine-rich C kinase substrate	120	121	14..601
M43	MAGP: microfibrillar-associated protein 2 precursor, transcript variant 1	122	123	115..666
M44	MAGP: microfibrillar-associated protein 2 precursor, transcript variant 2	124	125	100..651
M45	MAPK: mitogen-activated protein kinase 1	126	127	328..1410
M489	MCM6: minichromosome maintenance deficient (mis5, S. pombe) 6	128	129	62..2527
M46	MDK: midkine (neurite growth-promoting factor 2)	130	131	26..457
M47	MGP: matrix Gla protein	132	133	47..358
M48	MMP12: matrix metalloproteinase 12	134	135	13..1425
M49	MMP3: matrix metalloproteinase 3, stromelysin 1, progelatinase	136	137	64..1497
M294	MMP7: matrix metalloproteinase 7 (matrilysin, uterine), PUMP1 proteinase, variant 1	138	139	48..851
OV52	MMP7: matrix metalloproteinase 7 (matrilysin, uterine), PUMP1 proteinase, variant 2	140	139	28..831

M50	MMP9: matrix metalloproteinase 9, gelatinase B, 92kD gelatinase, 92kD type IV collagenase	141	142	20..2143
OV68	MSLN: mesothelin, variant 1	143	144	88..2196
OV69	MSLN: mesothelin, variant 2	145	146	88..1980
OV70	MSLN: mesothelin, variant 3	147	148	88..1950
OV71	MSLN: mesothelin, variant 4	149	150	88..2172
OV72	MSLN: mesothelin, variant 5	151	152	88..1926
OV43	MSLN: mesothelin, variant 6	153	154	88..1956
OV45	MUC1: mucin 1, transmembrane, variant 1	155	156	58..1605
M669	MUC1: mucin 1, transmembrane, variant 2	157	158	74..3841
M51	MYBL2: v-myb avian myeloblastosis viral oncogene homolog-like 2	159	160	128..2230
M52	MYH11: smooth muscle myosin heavy chain 11, isoform SM1	161	162	89..6007
M53	MYH11: smooth muscle myosin heavy chain 11, isoform SM2	163	164	89..5905
M54	NK4: natural killer cell transcript 4 , variant 1	165	166	60..764
M670	NK4: natural killer cell transcript 4 , variant 2	167	168	60..764
M55	NP25: (neuronal protein)	169	170	50..898
OV48	OPN-a (osteopontin), SPP1 (secreted phosphoprotein 1), bone sialoprotein I	171	172	1..942
OV49	OPN-b (osteopontin), SPP1 (secreted phosphoprotein 1), bone sialoprotein I	173	174	88..990
OV50	OPN-c (osteopontin), SPP1 (secreted phosphoprotein 1), bone sialoprotein I	175	176	1..861
M56	OSF-2, osteoblast specific factor 2 (fasciclin I-like), variant 1	177	178	12..2522
M491	OSF-2, osteoblast specific factor 2 (fasciclin I-like), variant 2	179	180	28..2367
M57	PIM2: pim-2 oncogene	181	182	186..1190
M58	PLAU: plasminogen activator, urokinase	183	184	77..1372
M59	PLK: polo (Drosophila)-like kinase	185	186	64..1875
M671	PNN: pinin, desmosome associated protein	187	188	31..2262
M60	PRG1: proteoglycan 1, secretory granule	189	190	25..501
M61	PTH1H: parathyroid hormone-like hormone	191	192	304..831
M62	PTN: pleiotrophin (heparin binding growth factor 8, neurite growth-promoting factor 1)	193	194	1542..2048
M63	RAB6KIFL: RAB6 interacting, kinesin-like (rabkinesin6)	195	196	28..2700
M64	RARRES3: retinoic acid receptor responder (tazarotene induced) 3	197	198	62..556
M65	RBP1: retinol-binding protein 1 (cellular), CRABP-I, CRBP-I	199	200	126..533
M66	RGS16: Regulator of G protein signaling-16	201	202	93..701
M67	S100A2: S100 calcium binding protein A2, variant 1	203	204	72..362
M68	S100A2: S100 calcium binding protein A2, variant 2	205	206	41..334
M69	SCYA20: small inducible cytokine subfamily A (Cys-Cys), member 20	207	208	59..349
M70	SPARC: Osteonectin (secreted protein, acidic, cysteine-rich)	209	210	58..969
M71	STCH: stress 70 protein chaperone, microsome-associated	211	212	37..1452
M492	STK12: serine/ threonine kinase 12	213	214	58..1092

M72	TK1: thymidine kinase 1, soluble	215	216	58..762
OV86	TMPRSS4: transmembrane protease, serine 4	217	218	310..1623
M73	TMSB4X: thymosin, beta 4, X chromosome	219	220	78..212
M74	TOP2A: topoisomerase (DNA) II alpha (170kD)	221	222	37..4632
M493	TPM1: tropomyosin 1 (alpha)	223	224	57..911
M75	TXN: thioredoxin	225	226	64..381
M76	UBCH10: ubiquitin carrier protein E2-C	227	228	41..580
M77	UBD: diubiquitin	229	230	19..516
M78	unnamed gene (1)	231	232	45..1353
M79	unnamed gene (2)	233	234	1..1508
M80	VATD: vacuolar proton pump delta polypeptide	235	236	166..909
M81	ZWINT: ZW10 interactor	237	238	25..858

Table 2

Marker	Gene Name	SEQ ID NO (nts)	SEQ ID NO (AAs)	CDS
M661	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 1	1	2	223..1194 6
M662	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 2	3	4	223..1192 2
M663	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 3	5	6	223..1200 0
M664	AKAP9: A kinase (PRKA) anchor protein (yotiao) 9, variant 4	7	8	223..1197 6
OV68	MSLN: mesothelin, variant 1	143	144	88..2196
OV69	MSLN: mesothelin, variant 2	145	146	88..1980
OV70	MSLN: mesothelin, variant 3	147	148	88..1950
OV71	MSLN: mesothelin, variant 4	149	150	88..2172
OV72	MSLN: mesothelin, variant 5	151	152	88..1926
M670	NK4: natural killer cell transcript 4 , variant 2	167	168	60..764
M67	S100A2: S100 calcium binding protein A2, variant 1	203	204	72..362
OV86	TMPRSS4: transmembrane protease, serine 4	217	218	310..1623
M78	unnamed gene (1)	231	232	45..1353
M79	unnamed gene (2)	233	234	1..1508

Table 3

Marker	Gene Name	SEQ ID NO (nts)	SEQ ID NO (AAs)	CDS
M481	EPPK1: epiplakin 1	51	52	89..15286
M482	FOSL2: FOS-like antigen 2, variant 1	65	66	324..1304
M483	FOSL2: FOS-like antigen 2, variant 2	67	66	324..1304
M484	FSHPRH1: FSH primary response (LRPR1, rat) homolog 1	68	69	270..2540
M35	ITGB6: integrin, beta 6	100	101	195..2561
OV43	MSLN: mesothelin, variant 6	153	154	88..1956

Definitions

5 As used herein, each of the following terms has the meaning associated with it in this section.

The articles "a" and "an" are used herein to refer to one or to more than one (*i.e.* to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

10 A "marker" is a gene whose altered level of expression in a tissue or cell from its expression level in normal or healthy tissue or cell is associated with a disease state, such as cancer. A "marker nucleic acid" is a nucleic acid (*e.g.*, mRNA, cDNA) encoded by or corresponding to a marker of the invention. Such marker nucleic acids include DNA (*e.g.*, cDNA) comprising the entire or a partial sequence of any of the
15 nucleic acid sequences set forth in the Sequence Listing or the complement of such a sequence. The marker nucleic acids also include RNA comprising the entire or a partial sequence of any of the nucleic acid sequences set forth in the Sequence Listing or the complement of such a sequence, wherein all thymidine residues are replaced with uridine residues. A "marker protein" is a protein encoded by or corresponding to a
20 marker of the invention. A marker protein comprises the entire or a partial sequence of any of the sequences set forth in the Sequence Listing. The terms "protein" and "polypeptide" are used interchangeably.

The term "probe" refers to any molecule which is capable of selectively binding to a specifically intended target molecule, for example, a nucleotide transcript or
25 protein encoded by or corresponding to a marker. Probes can be either synthesized by one skilled in the art, or derived from appropriate biological preparations. For purposes of detection of the target molecule, probes may be specifically designed to be labeled, as

described herein. Examples of molecules that can be utilized as probes include, but are not limited to, RNA, DNA, proteins, antibodies, and organic molecules.

A "cervical-associated" body fluid is a fluid which, when in the body of a patient, contacts or passes through cervical cells or into which cells or proteins shed
5 from cervical cells are capable of passing. The cells may be found in a cervical smear collected, for example, by a cervical brush. Exemplary cervical-associated body fluids include blood fluids, lymph, ascitic fluids, gynecological fluids, cystic fluid, urine, and fluids collected by vaginal rinsing.

The "normal" level of expression of a marker is the level of expression of
10 the marker in cervical cells of a human subject or patient not afflicted with cervical cancer

An "over-expression" or "significantly higher level of expression" of a marker refers to an expression level in a test sample that is greater than the standard error of the assay employed to assess expression, and is preferably at least twice, and
15 more preferably three, four, five or ten times the expression level of the marker in a control sample (*e.g.*, sample from a healthy subjects not having the marker associated disease) and preferably, the average expression level of the marker in several control samples.

A "significantly lower level of expression" of a marker refers to an
20 expression level in a test sample that is at least twice, and more preferably three, four, five or ten times lower than the expression level of the marker in a control sample (*e.g.*, sample from a healthy subject not having the marker associated disease) and preferably, the average expression level of the marker in several control samples.

As used herein, the term "promoter/regulatory sequence" means a nucleic
25 acid sequence which is required for expression of a gene product operably linked to the promoter/regulatory sequence. In some instances, this sequence may be the core promoter sequence and in other instances, this sequence may also include an enhancer sequence and other regulatory elements which are required for expression of the gene product. The promoter/regulatory sequence may, for example, be one which expresses
30 the gene product in a tissue-specific manner.

A "constitutive" promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a living human cell under most or all physiological conditions of the cell.

5 An "inducible" promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a living human cell substantially only when an inducer which corresponds to the promoter is present in the cell.

 A "tissue-specific" promoter is a nucleotide sequence which, when
10 operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a living human cell substantially only if the cell is a cell of the tissue type corresponding to the promoter.

 A "transcribed polynucleotide" or "nucleotide transcript" is a
polynucleotide (*e.g.* an mRNA, hnRNA, a cDNA, or an analog of such RNA or cDNA)
15 which is complementary to or homologous with all or a portion of a mature mRNA made by transcription of a marker of the invention and normal post-transcriptional processing (*e.g.* splicing), if any, of the RNA transcript, and reverse transcription of the RNA transcript.

 "Complementary" refers to the broad concept of sequence
20 complementarity between regions of two nucleic acid strands or between two regions of the same nucleic acid strand. It is known that an adenine residue of a first nucleic acid region is capable of forming specific hydrogen bonds ("base pairing") with a residue of a second nucleic acid region which is antiparallel to the first region if the residue is thymine or uracil. Similarly, it is known that a cytosine residue of a first nucleic acid
25 strand is capable of base pairing with a residue of a second nucleic acid strand which is antiparallel to the first strand if the residue is guanine. A first region of a nucleic acid is complementary to a second region of the same or a different nucleic acid if, when the two regions are arranged in an antiparallel fashion, at least one nucleotide residue of the first region is capable of base pairing with a residue of the second region. Preferably,
30 the first region comprises a first portion and the second region comprises a second portion, whereby, when the first and second portions are arranged in an antiparallel fashion, at least about 50%, and preferably at least about 75%, at least about 90%, or at least about 95% of the nucleotide residues of the first portion are capable of base pairing

with nucleotide residues in the second portion. More preferably, all nucleotide residues of the first portion are capable of base pairing with nucleotide residues in the second portion.

"Homologous" as used herein, refers to nucleotide sequence similarity
5 between two regions of the same nucleic acid strand or between regions of two different nucleic acid strands. When a nucleotide residue position in both regions is occupied by the same nucleotide residue, then the regions are homologous at that position. A first region is homologous to a second region if at least one nucleotide residue position of each region is occupied by the same residue. Homology between two regions is
10 expressed in terms of the proportion of nucleotide residue positions of the two regions that are occupied by the same nucleotide residue. By way of example, a region having the nucleotide sequence 5'-ATTGCC-3' and a region having the nucleotide sequence 5'-TATGGC-3' share 50% homology. Preferably, the first region comprises a first portion and the second region comprises a second portion, whereby, at least about 50%, and
15 preferably at least about 75%, at least about 90%, or at least about 95% of the nucleotide residue positions of each of the portions are occupied by the same nucleotide residue. More preferably, all nucleotide residue positions of each of the portions are occupied by the same nucleotide residue.

A molecule is "fixed" or "affixed" to a substrate if it is covalently or non-
20 covalently associated with the substrate such the substrate can be rinsed with a fluid (*e.g.* standard saline citrate, pH 7.4) without a substantial fraction of the molecule dissociating from the substrate.

As used herein, a "naturally-occurring" nucleic acid molecule refers to an RNA or DNA molecule having a nucleotide sequence that occurs in an organism found
25 in nature.

A cancer is "inhibited" if at least one symptom of the cancer is alleviated, terminated, slowed, or prevented. As used herein, cervical cancer is also "inhibited" if recurrence or metastasis of the cancer is reduced, slowed, delayed, or prevented.

A kit is any manufacture (*e.g.* a package or container) comprising at least
30 one reagent, *e.g.* a probe, for specifically detecting the expression of a marker of the invention. The kit may be promoted, distributed, or sold as a unit for performing the methods of the present invention.

“Proteins of the invention” encompass marker proteins and their fragments; variant marker proteins and their fragments; peptides and polypeptides comprising an at least 15 amino acid segment of a marker or variant marker protein; and fusion proteins comprising a marker or variant marker protein, or an at least 15 amino acid segment of a marker or variant marker protein.

Unless otherwise specified herewithin, the terms “antibody” and “antibodies” broadly encompass naturally-occurring forms of antibodies (*e.g.*, IgG, IgA, IgM, IgE) and recombinant antibodies such as single-chain antibodies, chimeric and humanized antibodies and multi-specific antibodies, as well as fragments and derivatives of all of the foregoing, which fragments and derivatives have at least an antigenic binding site. Antibody derivatives may comprise a protein or chemical moiety conjugated to an antibody.

Description

The present invention is based, in part, on newly identified markers which are over-expressed in cervical cancer cells as compared to their expression in normal (*i.e.* non-cancerous) cervical cells. The enhanced expression of one or more of these markers in cervical cells is herein correlated with the cancerous state of the tissue. The invention provides compositions, kits, and methods for assessing the cancerous state of cervical cells (*e.g.* cells obtained from a human, cultured human cells, archived or preserved human cells and *in vivo* cells) as well as treating patients afflicted with cervical cancer.

The compositions, kits, and methods of the invention have the following uses, among others:

- 1) assessing whether a patient is afflicted with cervical cancer;
- 2) assessing the stage of cervical cancer in a human patient;
- 3) assessing the grade of cervical cancer in a patient;
- 4) assessing the benign or malignant nature of cervical cancer in a patient;
- 5) assessing the metastatic potential of cervical cancer in a patient;
- 6) assessing the histological type of neoplasm associated with cervical cancer in a patient;

- 7) making antibodies, antibody fragments or antibody derivatives that are useful for treating cervical cancer and/or assessing whether a patient is afflicted with cervical cancer;
- 8) assessing the presence of cervical cancer cells;
- 5 9) assessing the efficacy of one or more test compounds for inhibiting cervical cancer in a patient;
- 10 10) assessing the efficacy of a therapy for inhibiting cervical cancer in a patient;
- 11) monitoring the progression of cervical cancer in a patient;
- 10 12) selecting a composition or therapy for inhibiting cervical cancer in a patient;
- 13) treating a patient afflicted with cervical cancer;
- 14) inhibiting cervical cancer in a patient;
- 15 15) assessing the cervical carcinogenic potential of a test compound; and
- 16) preventing the onset of cervical cancer in a patient at risk for developing cervical cancer.

The invention thus includes a method of assessing whether a patient is afflicted with cervical cancer which includes assessing whether the patient has pre-
20 metastasized cervical cancer. This method comprises comparing the level of expression of a marker of the invention (listed in Table 1) in a patient sample and the normal level of expression of the marker in a control, *e.g.*, a non-cervical cancer sample. A significantly higher level of expression of the marker in the patient sample as compared to the normal level is an indication that the patient is afflicted with cervical cancer.

25 Gene delivery vehicles, host cells and compositions (all described herein) containing nucleic acids comprising the entirety, or a segment of 15 or more nucleotides, of any of the nucleic acid sequences set forth in the Sequence Listing, or the complement of such sequences, and polypeptides comprising the entirety, or a segment of 10 or more amino acids, of any of the amino acid sequences set forth in the Sequence
30 Listing, are also provided by this invention.

As described herein, cervical cancer in patients is associated with an increased level of expression of one or more markers of the invention. While, as discussed above, some of these changes in expression level result from occurrence of the

cervical cancer, others of these changes induce, maintain, and promote the cancerous state of cervical cancer cells. Thus, cervical cancer characterized by an increase in the level of expression of one or more markers of the invention can be inhibited by reducing and/or interfering with the expression of the markers and/or function of the proteins encoded by those markers.

Expression of a marker of the invention can be inhibited in a number of ways generally known in the art. For example, an antisense oligonucleotide can be provided to the cervical cancer cells in order to inhibit transcription, translation, or both, of the marker(s). Alternately, a polynucleotide encoding an antibody, an antibody derivative, or an antibody fragment which specifically binds a marker protein, and operably linked with an appropriate promoter/regulator region, can be provided to the cell in order to generate intracellular antibodies which will inhibit the function or activity of the protein. The expression and/or function of a marker may also be inhibited by treating the cervical cancer cell with an antibody, antibody derivative or antibody fragment that specifically binds a marker protein. Using the methods described herein, a variety of molecules, particularly including molecules sufficiently small that they are able to cross the cell membrane, can be screened in order to identify molecules which inhibit expression of a marker or inhibit the function of a marker protein. The compound so identified can be provided to the patient in order to inhibit cervical cancer cells of the patient.

Any marker or combination of markers of the invention, as well as any known markers in combination with the markers of the invention, may be used in the compositions, kits, and methods of the present invention. In general, it is preferable to use markers for which the difference between the level of expression of the marker in cervical cancer cells and the level of expression of the same marker in normal cervical cells is as great as possible. Although this difference can be as small as the limit of detection of the method for assessing expression of the marker, it is preferred that the difference be at least greater than the standard error of the assessment method, and preferably a difference of at least 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 15-, 20-, 25-, 100-, 500-, 1000-fold or greater than the level of expression of the same marker in normal cervical tissue.

It is recognized that certain marker proteins are secreted from cervical cells (*i.e.* one or both of normal and cancerous cells) to the extracellular space surrounding the cells. These markers are preferably used in certain embodiments of the compositions, kits, and methods of the invention, owing to the fact that the such marker proteins can be detected in a cervical-associated body fluid sample, which may be more easily collected from a human patient than a tissue biopsy sample. In addition, preferred *in vivo* techniques for detection of a marker protein include introducing into a subject a labeled antibody directed against the protein. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

It is a simple matter for the skilled artisan to determine whether any particular marker protein is a secreted protein. In order to make this determination, the marker protein is expressed in, for example, a mammalian cell, preferably a human cervical cell line, extracellular fluid is collected, and the presence or absence of the protein in the extracellular fluid is assessed (*e.g.* using a labeled antibody which binds specifically with the protein).

The following is an example of a method which can be used to detect secretion of a protein. About 8×10^5 293T cells are incubated at 37°C in wells containing growth medium (Dulbecco's modified Eagle's medium {DMEM} supplemented with 10% fetal bovine serum) under a 5% (v/v) CO₂, 95% air atmosphere to about 60-70% confluence. The cells are then transfected using a standard transfection mixture comprising 2 micrograms of DNA comprising an expression vector encoding the protein and 10 microliters of LipofectAMINE™ (GIBCO/BRL Catalog no. 18342-012) per well. The transfection mixture is maintained for about 5 hours, and then replaced with fresh growth medium and maintained in an air atmosphere. Each well is gently rinsed twice with DMEM which does not contain methionine or cysteine (DMEM-MC; ICN Catalog no. 16-424-54). About 1 milliliter of DMEM-MC and about 50 microcuries of Trans-³⁵S™ reagent (ICN Catalog no. 51006) are added to each well. The wells are maintained under the 5% CO₂ atmosphere described above and incubated at 37°C for a selected period. Following incubation, 150 microliters of conditioned medium is removed and centrifuged to remove floating cells and debris.

The presence of the protein in the supernatant is an indication that the protein is secreted.

It will be appreciated that patient samples containing cervical cells may be used in the methods of the present invention. In these embodiments, the level of
5 expression of the marker can be assessed by assessing the amount (*e.g.* absolute amount or concentration) of the marker in a cervical cell sample, *e.g.*, cervical smear obtained from a patient. The cell sample can, of course, be subjected to a variety of well-known post-collection preparative and storage techniques (*e.g.*, nucleic acid and/or protein
10 extraction, fixation, storage, freezing, ultrafiltration, concentration, evaporation, centrifugation, etc.) prior to assessing the amount of the marker in the sample. Likewise, cervical smears may also be subjected to post-collection preparative and storage techniques, *e.g.*, fixation.

The compositions, kits, and methods of the invention can be used to detect expression of marker proteins having at least one portion which is displayed on
15 the surface of cells which express it. It is a simple matter for the skilled artisan to determine whether a marker protein, or a portion thereof, is exposed on the cell surface. For example, immunological methods may be used to detect such proteins on whole cells, or well known computer-based sequence analysis methods may be used to predict the presence of at least one extracellular domain (*i.e.* including both secreted proteins
20 and proteins having at least one cell-surface domain). Expression of a marker protein having at least one portion which is displayed on the surface of a cell which expresses it may be detected without necessarily lysing the cell (*e.g.* using a labeled antibody which binds specifically with a cell-surface domain of the protein).

Expression of a marker of the invention may be assessed by any of a wide
25 variety of well known methods for detecting expression of a transcribed nucleic acid or protein. Non-limiting examples of such methods include immunological methods for detection of secreted, cell-surface, cytoplasmic, or nuclear proteins, protein purification methods, protein function or activity assays, nucleic acid hybridization methods, nucleic acid reverse transcription methods, and nucleic acid amplification methods.

30 In a preferred embodiment, expression of a marker is assessed using an antibody (*e.g.* a radio-labeled, chromophore-labeled, fluorophore-labeled, or enzyme-labeled antibody), an antibody derivative (*e.g.* an antibody conjugated with a substrate or with the protein or ligand of a protein-ligand pair {*e.g.* biotin-streptavidin}), or an

antibody fragment (*e.g.* a single-chain antibody, an isolated antibody hypervariable domain, etc.) which binds specifically with a marker protein or fragment thereof, including a marker protein which has undergone all or a portion of its normal post-translational modification.

5 In another preferred embodiment, expression of a marker is assessed by preparing mRNA/cDNA (*i.e.* a transcribed polynucleotide) from cells in a patient sample, and by hybridizing the mRNA/cDNA with a reference polynucleotide which is a complement of a marker nucleic acid, or a fragment thereof. cDNA can, optionally, be amplified using any of a variety of polymerase chain reaction methods prior to
10 hybridization with the reference polynucleotide; preferably, it is not amplified. Expression of one or more markers can likewise be detected using quantitative PCR to assess the level of expression of the marker(s). Alternatively, any of the many known methods of detecting mutations or variants (*e.g.* single nucleotide polymorphisms, deletions, etc.) of a marker of the invention may be used to detect occurrence of a
15 marker in a patient.

 In a related embodiment, a mixture of transcribed polynucleotides obtained from the sample is contacted with a substrate having fixed thereto a polynucleotide complementary to or homologous with at least a portion (*e.g.* at least 7, 10, 15, 20, 25, 30, 40, 50, 100, 500, or more nucleotide residues) of a marker nucleic
20 acid. If polynucleotides complementary to or homologous with are differentially detectable on the substrate (*e.g.* detectable using different chromophores or fluorophores, or fixed to different selected positions), then the levels of expression of a plurality of markers can be assessed simultaneously using a single substrate (*e.g.* a "gene chip" microarray of polynucleotides fixed at selected positions). When a method of
25 assessing marker expression is used which involves hybridization of one nucleic acid with another, it is preferred that the hybridization be performed under stringent hybridization conditions.

 Because the compositions, kits, and methods of the invention rely on detection of a difference in expression levels of one or more markers of the invention, it
30 is preferable that the level of expression of the marker is significantly greater than the minimum detection limit of the method used to assess expression in at least one of normal cervical cells and cancerous cervical cells.

It is understood that by routine screening of additional patient samples using one or more of the markers of the invention, it will be realized that certain of the markers are over-expressed in cancers of various types, including specific cervical cancers, as well as other cancers such as breast cancer, ovarian cancer, etc. For example, it will be confirmed that some of the markers of the invention are over-expressed in most (*i.e.* 50% or more) or substantially all (*i.e.* 80% or more) of cervical cancer. Furthermore, it will be confirmed that certain of the markers of the invention are associated with cervical cancer of various stages (*i.e.* stage 0, I, II, III, and IV cervical cancers, as well as subclassifications IA1, IA2, IB, IB1, IB2, IIA, IIB, IIIA, IIIB, IVA, and IVB, using the FIGO Stage Grouping system for primary carcinoma of the cervix (see Gynecologic Oncology, 1991, 41:199 and Cancer, 1992, 69:482)), and pre-malignant conditions (*e.g.*, dysplasia including CIN or SIL), of various histologic subtypes (*e.g.* squamous cell carcinomas and squamous cell carcinoma variants such as verrucous carcinoma, lymphoepithelioma-like carcinoma, papillary squamous neoplasm and spindle cell squamous cell carcinoma (see Cervical Cancer and Preinvasive Neoplasia, 1996, pp. 90-91) serous, mucinous, endometrioid, and clear cell subtypes, as well as subclassifications and alternate classifications adenocarcinoma, papillary adenocarcinoma, papillary cystadenocarcinoma, surface papillary carcinoma, malignant adenofibroma, cystadenofibroma, adenocarcinoma, cystadenocarcinoma, adenoacanthoma, endometrioid stromal sarcoma, mesodermal {Müllerian} mixed tumor, malignant carcinoma, Brenner tumor, mixed epithelial tumor, and undifferentiated carcinoma, using the WHO/FIGO system for classification of malignant cervical tumors; Scully, *Atlas of Tumor Pathology*, 3d series, Washington DC), and various grades (*i.e.* grade I {well differentiated} , grade II {moderately well differentiated}, and grade III {poorly differentiated from surrounding normal tissue}). In addition, as a greater number of patient samples are assessed for expression of the markers of the invention and the outcomes of the individual patients from whom the samples were obtained are correlated, it will also be confirmed that altered expression of certain of the markers of the invention are strongly correlated with malignant cancers and that altered expression of other markers of the invention are strongly correlated with benign tumors. The compositions, kits, and methods of the invention are thus useful for characterizing one or more of the stage, grade, histological type, and benign/malignant nature of cervical cancer in patients.

When the compositions, kits, and methods of the invention are used for characterizing one or more of the stage, grade, histological type, and benign/malignant nature of cervical cancer in a patient, it is preferred that the marker or panel of markers of the invention is selected such that a positive result is obtained in at least about 20%,
5 and preferably at least about 40%, 60%, or 80%, and more preferably in substantially all patients afflicted with a cervical cancer of the corresponding stage, grade, histological type, or benign/malignant nature. Preferably, the marker or panel of markers of the invention is selected such that a positive predictive value (PPV) of greater than about 10% is obtained for the general population (more preferably coupled with an assay
10 specificity greater than 80%).

When a plurality of markers of the invention are used in the compositions, kits, and methods of the invention, the level of expression of each marker in a patient sample can be compared with the normal level of expression of each of the plurality of markers in non-cancerous samples of the same type, either in a single
15 reaction mixture (*i.e.* using reagents, such as different fluorescent probes, for each marker) or in individual reaction mixtures corresponding to one or more of the markers. In one embodiment, a significantly increased level of expression of more than one of the plurality of markers in the sample, relative to the corresponding normal levels, is an indication that the patient is afflicted with cervical cancer. When a plurality of markers
20 is used, it is preferred that 2, 3, 4, 5, 8, 10, 12, 15, 20, 30, or 50 or more individual markers be used, wherein fewer markers are preferred.

In order to maximize the sensitivity of the compositions, kits, and methods of the invention (*i.e.* by interference attributable to cells of non-cervical origin in a patient sample), it is preferable that the marker of the invention used therein be a
25 marker which has a restricted tissue distribution, *e.g.*, normally not expressed in a non-cervical tissue.

Only a small number of markers are known to be associated with cervical cancer (*e.g.* bcl-2, 15A8 antigen, cdc6, Mcm5, and EGFR). These markers are not, of course, included among the markers of the invention, although they may be used
30 together with one or more markers of the invention in a panel of markers, for example. It is well known that certain types of genes, such as oncogenes, tumor suppressor genes, growth factor-like genes, protease-like genes, and protein kinase-like genes are often involved with development of cancers of various types. Thus, among the markers of the

invention, use of those which correspond to proteins which resemble known proteins encoded by known oncogenes and tumor suppressor genes, and those which correspond to proteins which resemble growth factors, proteases, and protein kinases are preferred.

It is recognized that the compositions, kits, and methods of the invention
5 will be of particular utility to patients having an enhanced risk of developing cervical cancer and their medical advisors. Patients recognized as having an enhanced risk of developing cervical cancer include, for example, patients having a familial history of cervical cancer, patients identified as having a mutant oncogene (*i.e.* at least one allele), and patients of advancing age (*i.e.* women older than about 50 or 60 years).

10 The level of expression of a marker in normal (*i.e.* non-cancerous) human cervical tissue can be assessed in a variety of ways. In one embodiment, this normal level of expression is assessed by assessing the level of expression of the marker in a portion of cervical cells which appears to be non-cancerous and by comparing this normal level of expression with the level of expression in a portion of the cervical cells
15 which is suspected of being cancerous. Alternately, and particularly as further information becomes available as a result of routine performance of the methods described herein, population-average values for normal expression of the markers of the invention may be used. In other embodiments, the 'normal' level of expression of a marker may be determined by assessing expression of the marker in a patient sample
20 obtained from a non-cancer-afflicted patient, from a patient sample obtained from a patient before the suspected onset of cervical cancer in the patient, from archived patient samples, and the like.

The invention includes compositions, kits, and methods for assessing the presence of cervical cancer cells in a sample (*e.g.* an archived tissue sample or a sample
25 obtained from a patient). These compositions, kits, and methods are substantially the same as those described above, except that, where necessary, the compositions, kits, and methods are adapted for use with samples other than patient samples. For example, when the sample to be used is a parafinized, archived human tissue sample, it can be necessary to adjust the ratio of compounds in the compositions of the invention, in the
30 kits of the invention, or the methods used to assess levels of marker expression in the sample. Such methods are well known in the art and within the skill of the ordinary artisan.

The invention includes a kit for assessing the presence of cervical cancer cells (*e.g.* in a sample such as a patient sample). The kit comprises a plurality of reagents, each of which is capable of binding specifically with a marker nucleic acid or protein. Suitable reagents for binding with a marker protein include antibodies, antibody
5 derivatives, antibody fragments, and the like. Suitable reagents for binding with a marker nucleic acid (*e.g.* a genomic DNA, an mRNA, a spliced mRNA, a cDNA, or the like) include complementary nucleic acids. For example, the nucleic acid reagents may include oligonucleotides (labeled or non-labeled) fixed to a substrate, labeled
10 oligonucleotides not bound with a substrate, pairs of PCR primers, molecular beacon probes, and the like.

The kit of the invention may optionally comprise additional components useful for performing the methods of the invention. By way of example, the kit may comprise fluids (*e.g.* SSC buffer) suitable for annealing complementary nucleic acids or
for binding an antibody with a protein with which it specifically binds, one or more
15 sample compartments, an instructional material which describes performance of a method of the invention, a sample of normal cervical cells, a sample of cervical cancer cells, and the like.

The invention also includes a method of making an isolated hybridoma which produces an antibody useful for assessing whether patient is afflicted with an
20 cervical cancer. In this method, a protein or peptide comprising the entirety or a segment of a marker protein is synthesized or isolated (*e.g.* by purification from a cell in which it is expressed or by transcription and translation of a nucleic acid encoding the protein or peptide *in vivo* or *in vitro* using known methods). A vertebrate, preferably a mammal such as a mouse, rat, rabbit, or sheep, is immunized using the protein or
25 peptide. The vertebrate may optionally (and preferably) be immunized at least one additional time with the protein or peptide, so that the vertebrate exhibits a robust immune response to the protein or peptide. Splenocytes are isolated from the immunized vertebrate and fused with an immortalized cell line to form hybridomas, using any of a variety of methods well known in the art. Hybridomas formed in this
30 manner are then screened using standard methods to identify one or more hybridomas which produce an antibody which specifically binds with the marker protein or a fragment thereof. The invention also includes hybridomas made by this method and antibodies made using such hybridomas.

The invention also includes a method of assessing the efficacy of a test compound for inhibiting cervical cancer cells. As described above, differences in the level of expression of the markers of the invention correlate with the cancerous state of cervical cells. Although it is recognized that changes in the levels of expression of certain of the markers of the invention likely result from the cancerous state of cervical cells, it is likewise recognized that changes in the levels of expression of other of the markers of the invention induce, maintain, and promote the cancerous state of those cells. Thus, compounds which inhibit an cervical cancer in a patient will cause the level of expression of one or more of the markers of the invention to change to a level nearer the normal level of expression for that marker (*i.e.* the level of expression for the marker in non-cancerous cervical cells).

This method thus comprises comparing expression of a marker in a first cervical cell sample and maintained in the presence of the test compound and expression of the marker in a second cervical cell sample and maintained in the absence of the test compound. A significantly reduced expression of a marker of the invention in the presence of the test compound is an indication that the test compound inhibits cervical cancer. The cervical cell samples may, for example, be aliquots of a single sample of normal cervical cells obtained from a patient, pooled samples of normal cervical cells obtained from a patient, cells of a normal cervical cell line, aliquots of a single sample of cervical cancer cells obtained from a patient, pooled samples of cervical cancer cells obtained from a patient, cells of an cervical cancer cell line, or the like. In one embodiment, the samples are cervical cancer cells obtained from a patient and a plurality of compounds known to be effective for inhibiting various cervical cancers are tested in order to identify the compound which is likely to best inhibit the cervical cancer in the patient.

This method may likewise be used to assess the efficacy of a therapy for inhibiting cervical cancer in a patient. In this method, the level of expression of one or more markers of the invention in a pair of samples (one subjected to the therapy, the other not subjected to the therapy) is assessed. As with the method of assessing the efficacy of test compounds, if the therapy induces a significantly lower level of expression of a marker of the invention then the therapy is efficacious for inhibiting cervical cancer. As above, if samples from a selected patient are used in this method,

then alternative therapies can be assessed *in vitro* in order to select a therapy most likely to be efficacious for inhibiting cervical cancer in the patient.

As described above, the cancerous state of human cervical cells is correlated with changes in the levels of expression of the markers of the invention. The invention includes a method for assessing the human cervical cell carcinogenic potential of a test compound. This method comprises maintaining separate aliquots of human cervical cells in the presence and absence of the test compound. Expression of a marker of the invention in each of the aliquots is compared. A significantly higher level of expression of a marker of the invention in the aliquot maintained in the presence of the test compound (relative to the aliquot maintained in the absence of the test compound) is an indication that the test compound possesses human cervical cell carcinogenic potential. The relative carcinogenic potentials of various test compounds can be assessed by comparing the degree of enhancement or inhibition of the level of expression of the relevant markers, by comparing the number of markers for which the level of expression is enhanced or inhibited, or by comparing both.

Various aspects of the invention are described in further detail in the following subsections.

I. Isolated Nucleic Acid Molecules

One aspect of the invention pertains to isolated nucleic acid molecules, including nucleic acids which encode a marker protein or a portion thereof. Isolated nucleic acids of the invention also include nucleic acid molecules sufficient for use as hybridization probes to identify marker nucleic acid molecules, and fragments of marker nucleic acid molecules, *e.g.*, those suitable for use as PCR primers for the amplification or mutation of marker nucleic acid molecules. As used herein, the term "nucleic acid molecule" is intended to include DNA molecules (*e.g.*, cDNA or genomic DNA) and RNA molecules (*e.g.*, mRNA) and analogs of the DNA or RNA generated using nucleotide analogs. The nucleic acid molecule can be single-stranded or double-stranded, but preferably is double-stranded DNA.

An "isolated" nucleic acid molecule is one which is separated from other nucleic acid molecules which are present in the natural source of the nucleic acid molecule. Preferably, an "isolated" nucleic acid molecule is free of sequences (preferably protein-encoding sequences) which naturally flank the nucleic acid (*i.e.*,

sequences located at the 5' and 3' ends of the nucleic acid) in the genomic DNA of the organism from which the nucleic acid is derived. For example, in various embodiments, the isolated nucleic acid molecule can contain less than about 5 kB, 4 kB, 3 kB, 2 kB, 1 kB, 0.5 kB or 0.1 kB of nucleotide sequences which naturally flank the nucleic acid molecule in genomic DNA of the cell from which the nucleic acid is derived. Moreover, an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized.

10 A nucleic acid molecule of the present invention can be isolated using standard molecular biology techniques and the sequence information in the database records described herein. Using all or a portion of such nucleic acid sequences, nucleic acid molecules of the invention can be isolated using standard hybridization and cloning techniques (*e.g.*, as described in Sambrook *et al.*, ed., *Molecular Cloning: A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 15 1989).

 A nucleic acid molecule of the invention can be amplified using cDNA, mRNA, or genomic DNA as a template and appropriate oligonucleotide primers according to standard PCR amplification techniques. The nucleic acid so amplified can 20 be cloned into an appropriate vector and characterized by DNA sequence analysis. Furthermore, nucleotides corresponding to all or a portion of a nucleic acid molecule of the invention can be prepared by standard synthetic techniques, *e.g.*, using an automated DNA synthesizer.

 In another preferred embodiment, an isolated nucleic acid molecule of the 25 invention comprises a nucleic acid molecule which has a nucleotide sequence complementary to the nucleotide sequence of a marker nucleic acid or to the nucleotide sequence of a nucleic acid encoding a marker protein. A nucleic acid molecule which is complementary to a given nucleotide sequence is one which is sufficiently complementary to the given nucleotide sequence that it can hybridize to the given 30 nucleotide sequence thereby forming a stable duplex.

 Moreover, a nucleic acid molecule of the invention can comprise only a portion of a nucleic acid sequence, wherein the full length nucleic acid sequence comprises a marker nucleic acid or which encodes a marker protein. Such nucleic acids

can be used, for example, as a probe or primer. The probe/primer typically is used as one or more substantially purified oligonucleotides. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 7, preferably about 15, more preferably about 25, 50, 75, 100, 125, 150,
5 175, 200, 250, 300, 350, or 400 or more consecutive nucleotides of a nucleic acid of the invention.

Probes based on the sequence of a nucleic acid molecule of the invention can be used to detect transcripts or genomic sequences corresponding to one or more markers of the invention. The probe comprises a label group attached thereto, *e.g.*, a
10 radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Such probes can be used as part of a diagnostic test kit for identifying cells or tissues which mis-express the protein, such as by measuring levels of a nucleic acid molecule encoding the protein in a sample of cells from a subject, *e.g.*, detecting mRNA levels or determining whether a gene encoding the protein has been mutated or deleted.

15 The invention further encompasses nucleic acid molecules that differ, due to degeneracy of the genetic code, from the nucleotide sequence of nucleic acids encoding a marker protein (*e.g.*, a protein having one of the amino acid sequences set forth in the Sequence Listing), and thus encode the same protein.

It will be appreciated by those skilled in the art that DNA sequence
20 polymorphisms that lead to changes in the amino acid sequence can exist within a population (*e.g.*, the human population). Such genetic polymorphisms can exist among individuals within a population due to natural allelic variation. An allele is one of a group of genes which occur alternatively at a given genetic locus. In addition, it will be appreciated that DNA polymorphisms that affect RNA expression levels can also exist
25 that may affect the overall expression level of that gene (*e.g.*, by affecting regulation or degradation).

As used herein, the phrase "allelic variant" refers to a nucleotide sequence which occurs at a given locus or to a polypeptide encoded by the nucleotide sequence.

As used herein, the terms "gene" and "recombinant gene" refer to nucleic
30 acid molecules comprising an open reading frame encoding a polypeptide corresponding to a marker of the invention. Such natural allelic variations can typically result in 1-5% variance in the nucleotide sequence of a given gene. Alternative alleles can be identified by sequencing the gene of interest in a number of different individuals. This can be

readily carried out by using hybridization probes to identify the same genetic locus in a variety of individuals. Any and all such nucleotide variations and resulting amino acid polymorphisms or variations that are the result of natural allelic variation and that do not alter the functional activity are intended to be within the scope of the invention.

5 In another embodiment, an isolated nucleic acid molecule of the invention is at least 7, 15, 20, 25, 30, 40, 60, 80, 100, 150, 200, 250, 300, 350, 400, 450, 550, 650, 700, 800, 900, 1000, 1200, 1400, 1600, 1800, 2000, 2200, 2400, 2600, 2800, 3000, 3500, 4000, 4500, or more nucleotides in length and hybridizes under stringent conditions to a marker nucleic acid or to a nucleic acid encoding a marker protein. As
10 used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences at least 60% (65%, 70%, preferably 75%) identical to each other typically remain hybridized to each other. Such stringent conditions are known to those skilled in the art and can be found in sections 6.3.1-6.3.6 of *Current Protocols in Molecular Biology*, John Wiley & Sons,
15 N.Y. (1989). A preferred, non-limiting example of stringent hybridization conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 50-65°C.

In addition to naturally-occurring allelic variants of a nucleic acid molecule of the invention that can exist in the population, the skilled artisan will further
20 appreciate that sequence changes can be introduced by mutation thereby leading to changes in the amino acid sequence of the encoded protein, without altering the biological activity of the protein encoded thereby. For example, one can make nucleotide substitutions leading to amino acid substitutions at "non-essential" amino acid residues. A "non-essential" amino acid residue is a residue that can be altered from
25 the wild-type sequence without altering the biological activity, whereas an "essential" amino acid residue is required for biological activity. For example, amino acid residues that are not conserved or only semi-conserved among homologs of various species may be non-essential for activity and thus would be likely targets for alteration. Alternatively, amino acid residues that are conserved among the homologs of various
30 species (*e.g.*, murine and human) may be essential for activity and thus would not be likely targets for alteration.

Accordingly, another aspect of the invention pertains to nucleic acid molecules encoding a variant marker protein that contain changes in amino acid residues that are not essential for activity. Such variant marker proteins differ in amino acid sequence from the naturally-occurring marker proteins, yet retain biological activity. In one embodiment, such a variant marker protein has an amino acid sequence that is at least about 40% identical, 50%, 60%, 70%, 80%, 90%, 95%, or 98% identical to the amino acid sequence of a marker protein.

An isolated nucleic acid molecule encoding a variant marker protein can be created by introducing one or more nucleotide substitutions, additions or deletions into the nucleotide sequence of marker nucleic acids, such that one or more amino acid residue substitutions, additions, or deletions are introduced into the encoded protein. Mutations can be introduced by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Preferably, conservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), non-polar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Alternatively, mutations can be introduced randomly along all or part of the coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for biological activity to identify mutants that retain activity. Following mutagenesis, the encoded protein can be expressed recombinantly and the activity of the protein can be determined.

The present invention encompasses antisense nucleic acid molecules, *i.e.*, molecules which are complementary to a sense nucleic acid of the invention, *e.g.*, complementary to the coding strand of a double-stranded marker cDNA molecule or complementary to a marker mRNA sequence. Accordingly, an antisense nucleic acid of the invention can hydrogen bond to (*i.e.* anneal with) a sense nucleic acid of the invention. The antisense nucleic acid can be complementary to an entire coding strand,

or to only a portion thereof, *e.g.*, all or part of the protein coding region (or open reading frame). An antisense nucleic acid molecule can also be antisense to all or part of a non-coding region of the coding strand of a nucleotide sequence encoding a marker protein. The non-coding regions ("5' and 3' untranslated regions") are the 5' and 3' sequences
5 which flank the coding region and are not translated into amino acids.

An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 or more nucleotides in length. An antisense nucleic acid of the invention can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (*e.g.*, an
10 antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, *e.g.*, phosphorothioate derivatives and acridine substituted nucleotides can be used. Examples of modified nucleotides which
15 can be used to generate the antisense nucleic acid include 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-
20 methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-
25 methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been sub-cloned in an antisense orientation (*i.e.*, RNA transcribed from the inserted nucleic acid will be of an antisense
30 orientation to a target nucleic acid of interest, described further in the following subsection).

The antisense nucleic acid molecules of the invention are typically administered to a subject or generated *in situ* such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding a marker protein to thereby inhibit expression of the marker, *e.g.*, by inhibiting transcription and/or translation. The hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule which binds to DNA duplexes, through specific interactions in the major groove of the double helix. Examples of a route of administration of antisense nucleic acid molecules of the invention includes direct injection at a tissue site or infusion of the antisense nucleic acid into an ovary-associated body fluid. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then administered systemically. For example, for systemic administration, antisense molecules can be modified such that they specifically bind to receptors or antigens expressed on a selected cell surface, *e.g.*, by linking the antisense nucleic acid molecules to peptides or antibodies which bind to cell surface receptors or antigens. The antisense nucleic acid molecules can also be delivered to cells using the vectors described herein. To achieve sufficient intracellular concentrations of the antisense molecules, vector constructs in which the antisense nucleic acid molecule is placed under the control of a strong pol II or pol III promoter are preferred.

An antisense nucleic acid molecule of the invention can be an α -anomeric nucleic acid molecule. An α -anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual α -units, the strands run parallel to each other (Gaultier *et al.*, 1987, *Nucleic Acids Res.* 15:6625-6641). The antisense nucleic acid molecule can also comprise a 2'-O-methylribonucleotide (Inoue *et al.*, 1987, *Nucleic Acids Res.* 15:6131-6148) or a chimeric RNA-DNA analogue (Inoue *et al.*, 1987, *FEBS Lett.* 215:327-330).

The invention also encompasses ribozymes. Ribozymes are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (*e.g.*, hammerhead ribozymes as described in Haselhoff and Gerlach, 1988, *Nature* 334:585-591) can be used to catalytically cleave mRNA transcripts to thereby inhibit translation of the protein encoded by the mRNA. A ribozyme having specificity for a nucleic acid molecule encoding a marker protein can be designed based

upon the nucleotide sequence of a cDNA corresponding to the marker. For example, a derivative of a *Tetrahymena* L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved (see Cech *et al.* U.S. Patent No. 4,987,071; and Cech *et al.* U.S. Patent No. 5,116,742).

5 Alternatively, an mRNA encoding a polypeptide of the invention can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules (see, *e.g.*, Bartel and Szostak, 1993, *Science* 261:1411-1418).

The invention also encompasses nucleic acid molecules which form triple helical structures. For example, expression of a marker of the invention can be inhibited
10 by targeting nucleotide sequences complementary to the regulatory region of the gene encoding the marker nucleic acid or protein (*e.g.*, the promoter and/or enhancer) to form triple helical structures that prevent transcription of the gene in target cells. See generally Helene (1991) *Anticancer Drug Des.* 6(6):569-84; Helene (1992) *Ann. N.Y. Acad. Sci.* 660:27-36; and Maher (1992) *Bioassays* 14(12):807-15.

15 In various embodiments, the nucleic acid molecules of the invention can be modified at the base moiety, sugar moiety or phosphate backbone to improve, *e.g.*, the stability, hybridization, or solubility of the molecule. For example, the deoxyribose phosphate backbone of the nucleic acids can be modified to generate peptide nucleic acids (see Hyrup *et al.*, 1996, *Bioorganic & Medicinal Chemistry* 4(1): 5-23). As used
20 herein, the terms "peptide nucleic acids" or "PNAs" refer to nucleic acid mimics, *e.g.*, DNA mimics, in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral backbone of PNAs has been shown to allow for specific hybridization to DNA and RNA under conditions of low ionic strength. The synthesis of PNA oligomers can be
25 performed using standard solid phase peptide synthesis protocols as described in Hyrup *et al.* (1996), *supra*; Perry-O'Keefe *et al.* (1996) *Proc. Natl. Acad. Sci. USA* 93:14670-675.

PNAs can be used in therapeutic and diagnostic applications. For example, PNAs can be used as antisense or antigene agents for sequence-specific
30 modulation of gene expression by, *e.g.*, inducing transcription or translation arrest or inhibiting replication. PNAs can also be used, *e.g.*, in the analysis of single base pair mutations in a gene by, *e.g.*, PNA directed PCR clamping; as artificial restriction enzymes when used in combination with other enzymes, *e.g.*, S1 nucleases (Hyrup

(1996), *supra*; or as probes or primers for DNA sequence and hybridization (Hyrup, 1996, *supra*; Perry-O'Keefe *et al.*, 1996, *Proc. Natl. Acad. Sci. USA* 93:14670-675).

In another embodiment, PNAs can be modified, *e.g.*, to enhance their stability or cellular uptake, by attaching lipophilic or other helper groups to PNA, by the formation of PNA-DNA chimeras, or by the use of liposomes or other techniques of drug delivery known in the art. For example, PNA-DNA chimeras can be generated which can combine the advantageous properties of PNA and DNA. Such chimeras allow DNA recognition enzymes, *e.g.*, RNase H and DNA polymerases, to interact with the DNA portion while the PNA portion would provide high binding affinity and specificity. PNA-DNA chimeras can be linked using linkers of appropriate lengths selected in terms of base stacking, number of bonds between the nucleobases, and orientation (Hyrup, 1996, *supra*). The synthesis of PNA-DNA chimeras can be performed as described in Hyrup (1996), *supra*, and Finn *et al.* (1996) *Nucleic Acids Res.* 24(17):3357-63. For example, a DNA chain can be synthesized on a solid support using standard phosphoramidite coupling chemistry and modified nucleoside analogs. Compounds such as 5'-(4-methoxytrityl)amino-5'-deoxy-thymidine phosphoramidite can be used as a link between the PNA and the 5' end of DNA (Mag *et al.*, 1989, *Nucleic Acids Res.* 17:5973-88). PNA monomers are then coupled in a step-wise manner to produce a chimeric molecule with a 5' PNA segment and a 3' DNA segment (Finn *et al.*, 1996, *Nucleic Acids Res.* 24(17):3357-63). Alternatively, chimeric molecules can be synthesized with a 5' DNA segment and a 3' PNA segment (Peterser *et al.*, 1975, *Bioorganic Med. Chem. Lett.* 5:1119-1124).

In other embodiments, the oligonucleotide can include other appended groups such as peptides (*e.g.*, for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, *e.g.*, Letsinger *et al.*, 1989, *Proc. Natl. Acad. Sci. USA* 86:6553-6556; Lemaitre *et al.*, 1987, *Proc. Natl. Acad. Sci. USA* 84:648-652; PCT Publication No. WO 88/09810) or the blood-brain barrier (see, *e.g.*, PCT Publication No. WO 89/10134). In addition, oligonucleotides can be modified with hybridization-triggered cleavage agents (see, *e.g.*, Krol *et al.*, 1988, *Bio/Techniques* 6:958-976) or intercalating agents (see, *e.g.*, Zon, 1988, *Pharm. Res.* 5:539-549). To this end, the oligonucleotide can be conjugated to another molecule, *e.g.*, a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

The invention also includes molecular beacon nucleic acids having at least one region which is complementary to a nucleic acid of the invention, such that the molecular beacon is useful for quantitating the presence of the nucleic acid of the invention in a sample. A "molecular beacon" nucleic acid is a nucleic acid comprising a pair of complementary regions and having a fluorophore and a fluorescent quencher associated therewith. The fluorophore and quencher are associated with different portions of the nucleic acid in such an orientation that when the complementary regions are annealed with one another, fluorescence of the fluorophore is quenched by the quencher. When the complementary regions of the nucleic acid are not annealed with one another, fluorescence of the fluorophore is quenched to a lesser degree. Molecular beacon nucleic acids are described, for example, in U.S. Patent 5,876,930.

II. Isolated Proteins and Antibodies

One aspect of the invention pertains to isolated marker proteins and biologically active portions thereof, as well as polypeptide fragments suitable for use as immunogens to raise antibodies directed against a marker protein or a fragment thereof. In one embodiment, the native marker protein can be isolated from cells or tissue sources by an appropriate purification scheme using standard protein purification techniques. In another embodiment, a protein or peptide comprising the whole or a segment of the marker protein is produced by recombinant DNA techniques. Alternative to recombinant expression, such protein or peptide can be synthesized chemically using standard peptide synthesis techniques.

An "isolated" or "purified" protein or biologically active portion thereof is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the protein is derived, or substantially free of chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of protein in which the protein is separated from cellular components of the cells from which it is isolated or recombinantly produced. Thus, protein that is substantially free of cellular material includes preparations of protein having less than about 30%, 20%, 10%, or 5% (by dry weight) of heterologous protein (also referred to herein as a "contaminating protein"). When the protein or biologically active portion thereof is recombinantly produced, it is also preferably substantially free of culture medium, *i.e.*, culture medium represents less

than about 20%, 10%, or 5% of the volume of the protein preparation. When the protein is produced by chemical synthesis, it is preferably substantially free of chemical precursors or other chemicals, *i.e.*, it is separated from chemical precursors or other chemicals which are involved in the synthesis of the protein. Accordingly such
5 preparations of the protein have less than about 30%, 20%, 10%, 5% (by dry weight) of chemical precursors or compounds other than the polypeptide of interest.

Biologically active portions of a marker protein include polypeptides comprising amino acid sequences sufficiently identical to or derived from the amino acid sequence of the marker protein, which include fewer amino acids than the full
10 length protein, and exhibit at least one activity of the corresponding full-length protein. Typically, biologically active portions comprise a domain or motif with at least one activity of the corresponding full-length protein. A biologically active portion of a marker protein of the invention can be a polypeptide which is, for example, 10, 25, 50, 100 or more amino acids in length. Moreover, other biologically active portions, in
15 which other regions of the marker protein are deleted, can be prepared by recombinant techniques and evaluated for one or more of the functional activities of the native form of the marker protein.

Preferred marker proteins are encoded by nucleotide sequences comprising the sequence of any of the sequences set forth in the Sequence Listing.
20 Other useful proteins are substantially identical (*e.g.*, at least about 40%, preferably 50%, 60%, 70%, 80%, 90%, 95%, or 99%) to one of these sequences and retain the functional activity of the corresponding naturally-occurring marker protein yet differ in amino acid sequence due to natural allelic variation or mutagenesis.

To determine the percent identity of two amino acid sequences or of two
25 nucleic acids, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid
30 residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, %

identity = # of identical positions/total # of positions (*e.g.*, overlapping positions) x100).
In one embodiment the two sequences are the same length.

The determination of percent identity between two sequences can be accomplished using a mathematical algorithm. A preferred, non-limiting example of a
5 mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul (1990) *Proc. Natl. Acad. Sci. USA* 87:2264-2268, modified as in Karlin and Altschul (1993) *Proc. Natl. Acad. Sci. USA* 90:5873-5877. Such an algorithm is incorporated into the BLASTN and BLASTX programs of Altschul, *et al.* (1990) *J. Mol. Biol.* 215:403-410. BLAST nucleotide searches can be performed with
10 the BLASTN program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the invention. BLAST protein searches can be performed with the BLASTP program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to a protein molecules of the invention. To obtain gapped alignments for comparison purposes, a newer version of the BLAST algorithm called
15 Gapped BLAST can be utilized as described in Altschul *et al.* (1997) *Nucleic Acids Res.* 25:3389-3402, which is able to perform gapped local alignments for the programs BLASTN, BLASTP and BLASTX. Alternatively, PSI-Blast can be used to perform an iterated search which detects distant relationships between molecules. When utilizing BLAST, Gapped BLAST, and PSI-Blast programs, the default parameters of the
20 respective programs (*e.g.*, BLASTX and BLASTN) can be used. See <http://www.ncbi.nlm.nih.gov>. Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, (1988) *CABIOS* 4:11-17. Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software
25 package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. Yet another useful algorithm for identifying regions of local sequence similarity and alignment is the FASTA algorithm as described in Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85:2444-2448. When using the FASTA algorithm for
30 comparing nucleotide or amino acid sequences, a PAM120 weight residue table can, for example, be used with a *k*-tuple value of 2.

The percent identity between two sequences can be determined using techniques similar to those described above, with or without allowing gaps. In calculating percent identity, only exact matches are counted.

The invention also provides chimeric or fusion proteins comprising a
5 marker protein or a segment thereof. As used herein, a "chimeric protein" or "fusion protein" comprises all or part (preferably a biologically active part) of a marker protein operably linked to a heterologous polypeptide (*i.e.*, a polypeptide other than the marker protein). Within the fusion protein, the term "operably linked" is intended to indicate that the marker protein or segment thereof and the heterologous polypeptide are fused
10 in-frame to each other. The heterologous polypeptide can be fused to the amino-terminus or the carboxyl-terminus of the marker protein or segment.

One useful fusion protein is a GST fusion protein in which a marker protein or segment is fused to the carboxyl terminus of GST sequences. Such fusion proteins can facilitate the purification of a recombinant polypeptide of the invention.

15 In another embodiment, the fusion protein contains a heterologous signal sequence at its amino terminus. For example, the native signal sequence of a marker protein can be removed and replaced with a signal sequence from another protein. For example, the gp67 secretory sequence of the baculovirus envelope protein can be used as a heterologous signal sequence (Ausubel *et al.*, ed., *Current Protocols in Molecular*
20 *Biology*, John Wiley & Sons, NY, 1992). Other examples of eukaryotic heterologous signal sequences include the secretory sequences of melittin and human placental alkaline phosphatase (Stratagene; La Jolla, California). In yet another example, useful prokaryotic heterologous signal sequences include the phoA secretory signal (Sambrook
25 *et al.*, *supra*) and the protein A secretory signal (Pharmacia Biotech; Piscataway, New Jersey).

In yet another embodiment, the fusion protein is an immunoglobulin fusion protein in which all or part of a marker protein is fused to sequences derived from a member of the immunoglobulin protein family. The immunoglobulin fusion proteins of the invention can be incorporated into pharmaceutical compositions and administered
30 to a subject to inhibit an interaction between a ligand (soluble or membrane-bound) and a protein on the surface of a cell (receptor), to thereby suppress signal transduction *in vivo*. The immunoglobulin fusion protein can be used to affect the bioavailability of a cognate ligand of a marker protein. Inhibition of ligand/receptor interaction can be

useful therapeutically, both for treating proliferative and differentiative disorders and for modulating (*e.g.* promoting or inhibiting) cell survival. Moreover, the immunoglobulin fusion proteins of the invention can be used as immunogens to produce antibodies directed against a marker protein in a subject, to purify ligands and in screening assays
5 to identify molecules which inhibit the interaction of the marker protein with ligands.

Chimeric and fusion proteins of the invention can be produced by standard recombinant DNA techniques. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor
10 primers which give rise to complementary overhangs between two consecutive gene fragments which can subsequently be annealed and re-amplified to generate a chimeric gene sequence (see, *e.g.*, Ausubel *et al.*, *supra*). Moreover, many expression vectors are commercially available that already encode a fusion moiety (*e.g.*, a GST polypeptide). A nucleic acid encoding a polypeptide of the invention can be cloned into such an
15 expression vector such that the fusion moiety is linked in-frame to the polypeptide of the invention.

A signal sequence can be used to facilitate secretion and isolation of marker proteins. Signal sequences are typically characterized by a core of hydrophobic amino acids which are generally cleaved from the mature protein during secretion in one
20 or more cleavage events. Such signal peptides contain processing sites that allow cleavage of the signal sequence from the mature proteins as they pass through the secretory pathway. Thus, the invention pertains to marker proteins, fusion proteins or segments thereof having a signal sequence, as well as to such proteins from which the signal sequence has been proteolytically cleaved (*i.e.*, the cleavage products). In one
25 embodiment, a nucleic acid sequence encoding a signal sequence can be operably linked in an expression vector to a protein of interest, such as a marker protein or a segment thereof. The signal sequence directs secretion of the protein, such as from a eukaryotic host into which the expression vector is transformed, and the signal sequence is subsequently or concurrently cleaved. The protein can then be readily purified from the
30 extracellular medium by art recognized methods. Alternatively, the signal sequence can be linked to the protein of interest using a sequence which facilitates purification, such as with a GST domain.

The present invention also pertains to variants of the marker proteins. Such variants have an altered amino acid sequence which can function as either agonists (mimetics) or as antagonists. Variants can be generated by mutagenesis, *e.g.*, discrete point mutation or truncation. An agonist can retain substantially the same, or a subset,
5 of the biological activities of the naturally occurring form of the protein. An antagonist of a protein can inhibit one or more of the activities of the naturally occurring form of the protein by, for example, competitively binding to a downstream or upstream member of a cellular signaling cascade which includes the protein of interest. Thus, specific biological effects can be elicited by treatment with a variant of limited function.

10 Treatment of a subject with a variant having a subset of the biological activities of the naturally occurring form of the protein can have fewer side effects in a subject relative to treatment with the naturally occurring form of the protein.

Variants of a marker protein which function as either agonists (mimetics) or as antagonists can be identified by screening combinatorial libraries of mutants, *e.g.*,
15 truncation mutants, of the protein of the invention for agonist or antagonist activity. In one embodiment, a variegated library of variants is generated by combinatorial mutagenesis at the nucleic acid level and is encoded by a variegated gene library. A variegated library of variants can be produced by, for example, enzymatically ligating a mixture of synthetic oligonucleotides into gene sequences such that a degenerate set of
20 potential protein sequences is expressible as individual polypeptides, or alternatively, as a set of larger fusion proteins (*e.g.*, for phage display). There are a variety of methods which can be used to produce libraries of potential variants of the marker proteins from a degenerate oligonucleotide sequence. Methods for synthesizing degenerate oligonucleotides are known in the art (see, *e.g.*, Narang, 1983, *Tetrahedron* 39:3; Itakura
25 *et al.*, 1984, *Annu. Rev. Biochem.* 53:323; Itakura *et al.*, 1984, *Science* 198:1056; Ike *et al.*, 1983 *Nucleic Acid Res.* 11:477).

In addition, libraries of segments of a marker protein can be used to generate a variegated population of polypeptides for screening and subsequent selection of variant marker proteins or segments thereof. For example, a library of coding
30 sequence fragments can be generated by treating a double stranded PCR fragment of the coding sequence of interest with a nuclease under conditions wherein nicking occurs only about once per molecule, denaturing the double stranded DNA, renaturing the DNA to form double stranded DNA which can include sense/antisense pairs from different

nicked products, removing single stranded portions from reformed duplexes by treatment with S1 nuclease, and ligating the resulting fragment library into an expression vector. By this method, an expression library can be derived which encodes amino terminal and internal fragments of various sizes of the protein of interest.

5 Several techniques are known in the art for screening gene products of combinatorial libraries made by point mutations or truncation, and for screening cDNA libraries for gene products having a selected property. The most widely used techniques, which are amenable to high through-put analysis, for screening large gene libraries typically include cloning the gene library into replicable expression vectors,
10 transforming appropriate cells with the resulting library of vectors, and expressing the combinatorial genes under conditions in which detection of a desired activity facilitates isolation of the vector encoding the gene whose product was detected. Recursive ensemble mutagenesis (REM), a technique which enhances the frequency of functional mutants in the libraries, can be used in combination with the screening assays to identify
15 variants of a protein of the invention (Arkin and Yourvan, 1992, *Proc. Natl. Acad. Sci. USA* 89:7811-7815; Delgrave *et al.*, 1993, *Protein Engineering* 6(3):327- 331).

 Another aspect of the invention pertains to antibodies directed against a protein of the invention. In preferred embodiments, the antibodies specifically bind a marker protein or a fragment thereof. The terms "antibody" and "antibodies" as used
20 interchangeably herein refer to immunoglobulin molecules as well as fragments and derivatives thereof that comprise an immunologically active portion of an immunoglobulin molecule, (*i.e.*, such a portion contains an antigen binding site which specifically binds an antigen, such as a marker protein, *e.g.*, an epitope of a marker protein). An antibody which specifically binds to a protein of the invention is an
25 antibody which binds the protein, but does not substantially bind other molecules in a sample, *e.g.*, a biological sample, which naturally contains the protein. Examples of an immunologically active portion of an immunoglobulin molecule include, but are not limited to, single-chain antibodies (scAb), F(ab) and F(ab')₂ fragments.

 An isolated protein of the invention or a fragment thereof can be used as
30 an immunogen to generate antibodies. The full-length protein can be used or, alternatively, the invention provides antigenic peptide fragments for use as immunogens. The antigenic peptide of a protein of the invention comprises at least 8 (preferably 10, 15, 20, or 30 or more) amino acid residues of the amino acid sequence of one of the

proteins of the invention, and encompasses at least one epitope of the protein such that an antibody raised against the peptide forms a specific immune complex with the protein. Preferred epitopes encompassed by the antigenic peptide are regions that are located on the surface of the protein, *e.g.*, hydrophilic regions. Hydrophobicity sequence analysis, hydrophilicity sequence analysis, or similar analyses can be used to identify hydrophilic regions. In preferred embodiments, an isolated marker protein or fragment thereof is used as an immunogen.

An immunogen typically is used to prepare antibodies by immunizing a suitable (*i.e.* immunocompetent) subject such as a rabbit, goat, mouse, or other mammal or vertebrate. An appropriate immunogenic preparation can contain, for example, recombinantly-expressed or chemically-synthesized protein or peptide. The preparation can further include an adjuvant, such as Freund's complete or incomplete adjuvant, or a similar immunostimulatory agent. Preferred immunogen compositions are those that contain no other human proteins such as, for example, immunogen compositions made using a non-human host cell for recombinant expression of a protein of the invention. In such a manner, the resulting antibody compositions have reduced or no binding of human proteins other than a protein of the invention.

The invention provides polyclonal and monoclonal antibodies. The term "monoclonal antibody" or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a particular epitope. Preferred polyclonal and monoclonal antibody compositions are ones that have been selected for antibodies directed against a protein of the invention. Particularly preferred polyclonal and monoclonal antibody preparations are ones that contain only antibodies directed against a marker protein or fragment thereof.

Polyclonal antibodies can be prepared by immunizing a suitable subject with a protein of the invention as an immunogen. The antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized polypeptide. At an appropriate time after immunization, *e.g.*, when the specific antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies (mAb) by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein (1975) *Nature* 256:495-497, the human B cell

hybridoma technique (see Kozbor *et al.*, 1983, *Immunol. Today* 4:72), the EBV-hybridoma technique (see Cole *et al.*, pp. 77-96 In *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., 1985) or trioma techniques. The technology for producing hybridomas is well known (see generally *Current Protocols in Immunology*, Coligan *et al.* ed., John Wiley & Sons, New York, 1994). Hybridoma cells producing a
5 monoclonal antibody of the invention are detected by screening the hybridoma culture supernatants for antibodies that bind the polypeptide of interest, *e.g.*, using a standard ELISA assay.

Alternative to preparing monoclonal antibody-secreting hybridomas, a
10 monoclonal antibody directed against a protein of the invention can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (*e.g.*, an antibody phage display library) with the polypeptide of interest. Kits for generating and screening phage display libraries are commercially available (*e.g.*, the Pharmacia *Recombinant Phage Antibody System*, Catalog No. 27-9400-01; and the Stratagene
15 *SurfZAP Phage Display Kit*, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, U.S. Patent No. 5,223,409; PCT Publication No. WO 92/18619; PCT Publication No. WO 91/17271; PCT Publication No. WO 92/20791; PCT Publication No. WO 92/15679; PCT Publication No. WO 93/01288; PCT
20 Publication No. WO 92/01047; PCT Publication No. WO 92/09690; PCT Publication No. WO 90/02809; Fuchs *et al.* (1991) *Bio/Technology* 9:1370-1372; Hay *et al.* (1992) *Hum. Antibod. Hybridomas* 3:81-85; Huse *et al.* (1989) *Science* 246:1275-1281; Griffiths *et al.* (1993) *EMBO J.* 12:725-734.

The invention also provides recombinant antibodies that specifically bind
25 a protein of the invention. In preferred embodiments, the recombinant antibodies specifically binds a marker protein or fragment thereof. Recombinant antibodies include, but are not limited to, chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, single-chain antibodies and multi-specific antibodies. A chimeric antibody is a molecule in which different portions are
30 derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region. (See, *e.g.*, Cabilly *et al.*, U.S. Patent No. 4,816,567; and Boss *et al.*, U.S. Patent No. 4,816,397, which are incorporated herein by reference in their entirety.) Single-chain antibodies have an

antigen binding site and consist of a single polypeptide. They can be produced by techniques known in the art, for example using methods described in Ladner *et al.* U.S. Pat. No. 4,946,778 (which is incorporated herein by reference in its entirety); Bird *et al.*, (1988) *Science* 242:423-426; Whitlow *et al.*, (1991) *Methods in Enzymology* 2:1-9; 5 Whitlow *et al.*, (1991) *Methods in Enzymology* 2:97-105; and Huston *et al.*, (1991) *Methods in Enzymology Molecular Design and Modeling: Concepts and Applications* 203:46-88. Multi-specific antibodies are antibody molecules having at least two antigen-binding sites that specifically bind different antigens. Such molecules can be produced by techniques known in the art, for example using methods described in Segal, 10 U.S. Patent No. 4,676,980 (the disclosure of which is incorporated herein by reference in its entirety); Holliger *et al.*, (1993) *Proc. Natl. Acad. Sci. USA* 90:6444-6448; Whitlow *et al.*, (1994) *Protein Eng.* 7:1017-1026 and U.S. Pat. No. 6,121,424.

Humanized antibodies are antibody molecules from non-human species having one or more complementarity determining regions (CDRs) from the non-human 15 species and a framework region from a human immunoglobulin molecule. (See, *e.g.*, Queen, U.S. Patent No. 5,585,089, which is incorporated herein by reference in its entirety.) Humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in PCT Publication No. WO 87/02671; European Patent Application 184,187; European Patent Application 20 171,496; European Patent Application 173,494; PCT Publication No. WO 86/01533; U.S. Patent No. 4,816,567; European Patent Application 125,023; Better *et al.* (1988) *Science* 240:1041-1043; Liu *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:3439-3443; Liu *et al.* (1987) *J. Immunol.* 139:3521-3526; Sun *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:214-218; Nishimura *et al.* (1987) *Cancer Res.* 47:999-1005; Wood *et al.* (1985) 25 *Nature* 314:446-449; and Shaw *et al.* (1988) *J. Natl. Cancer Inst.* 80:1553-1559; Morrison (1985) *Science* 229:1202-1207; Oi *et al.* (1986) *Bio/Techniques* 4:214; U.S. Patent 5,225,539; Jones *et al.* (1986) *Nature* 321:552-525; Verhoeyan *et al.* (1988) *Science* 239:1534; and Beidler *et al.* (1988) *J. Immunol.* 141:4053-4060.

More particularly, humanized antibodies can be produced, for example, 30 using transgenic mice which are incapable of expressing endogenous immunoglobulin heavy and light chains genes, but which can express human heavy and light chain genes. The transgenic mice are immunized in the normal fashion with a selected antigen, *e.g.*, all or a portion of a polypeptide corresponding to a marker of the invention. Monoclonal

antibodies directed against the antigen can be obtained using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically
5 useful IgG, IgA and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar (1995) *Int. Rev. Immunol.* 13:65-93). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, *e.g.*, U.S. Patent 5,625,126; U.S. Patent 5,633,425; U.S. Patent 5,569,825; U.S. Patent 5,661,016;
10 and U.S. Patent 5,545,806. In addition, companies such as Abgenix, Inc. (Freemont, CA), can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected
15 non-human monoclonal antibody, *e.g.*, a murine antibody, is used to guide the selection of a completely human antibody recognizing the same epitope (Jespers *et al.*, 1994, *Bio/technology* 12:899-903).

The antibodies of the invention can be isolated after production (*e.g.*, from the blood or serum of the subject) or synthesis and further purified by well-known
20 techniques. For example, IgG antibodies can be purified using protein A chromatography. Antibodies specific for a protein of the invention can be selected or (*e.g.*, partially purified) or purified by, *e.g.*, affinity chromatography. For example, a recombinantly expressed and purified (or partially purified) protein of the invention is produced as described herein, and covalently or non-covalently coupled to a solid
25 support such as, for example, a chromatography column. The column can then be used to affinity purify antibodies specific for the proteins of the invention from a sample containing antibodies directed against a large number of different epitopes, thereby generating a substantially purified antibody composition, *i.e.*, one that is substantially free of contaminating antibodies. By a substantially purified antibody composition is
30 meant, in this context, that the antibody sample contains at most only 30% (by dry weight) of contaminating antibodies directed against epitopes other than those of the desired protein of the invention, and preferably at most 20%, yet more preferably at most 10%, and most preferably at most 5% (by dry weight) of the sample is

contaminating antibodies. A purified antibody composition means that at least 99% of the antibodies in the composition are directed against the desired protein of the invention.

In a preferred embodiment, the substantially purified antibodies of the invention may specifically bind to a signal peptide, a secreted sequence, an extracellular domain, a transmembrane or a cytoplasmic domain or cytoplasmic membrane of a protein of the invention. In a particularly preferred embodiment, the substantially purified antibodies of the invention specifically bind to a secreted sequence or an extracellular domain of the amino acid sequences of a protein of the invention. In a more preferred embodiment, the substantially purified antibodies of the invention specifically bind to a secreted sequence or an extracellular domain of the amino acid sequences of a marker protein.

An antibody directed against a protein of the invention can be used to isolate the protein by standard techniques, such as affinity chromatography or immunoprecipitation. Moreover, such an antibody can be used to detect the marker protein or fragment thereof (*e.g.*, in a cellular lysate or cell supernatant) in order to evaluate the level and pattern of expression of the marker. The antibodies can also be used diagnostically to monitor protein levels in tissues or body fluids (*e.g.* in a cervical-associated body fluid) as part of a clinical testing procedure, *e.g.*, to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by the use of an antibody derivative, which comprises an antibody of the invention coupled to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β -galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I , ^{131}I , ^{35}S or ^3H .

Antibodies of the invention may also be used as therapeutic agents in treating cancers. In a preferred embodiment, completely human antibodies of the invention are used for therapeutic treatment of human cancer patients, particularly those having an cervical cancer. In another preferred embodiment, antibodies that bind
5 specifically to a marker protein or fragment thereof are used for therapeutic treatment. Further, such therapeutic antibody may be an antibody derivative or immunotoxin comprising an antibody conjugated to a therapeutic moiety such as a cytotoxin, a therapeutic agent or a radioactive metal ion. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include taxol, cytochalasin B, gramicidin D,
10 ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (*e.g.*, methotrexate,
15 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (*e.g.*, mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (*e.g.*, daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (*e.g.*,
20 dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (*e.g.*, vincristine and vinblastine).

The conjugated antibodies of the invention can be used for modifying a given biological response, for the drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or
25 polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as ribosome-inhibiting protein (see Better et al., U.S. Patent No. 6,146,631, the disclosure of which is incorporated herein in its entirety), abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, .alpha.-interferon, .beta.-interferon, nerve growth factor, platelet derived growth factor,
30 tissue plasminogen activator; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

Techniques for conjugating such therapeutic moiety to antibodies are well known, see, *e.g.*, Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug
5 Delivery", in *Controlled Drug Delivery* (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in *Monoclonal Antibodies '84: Biological And Clinical Applications*, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in
10 *Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", *Immunol. Rev.*, 62:119-58 (1982).

Accordingly, in one aspect, the invention provides substantially purified antibodies, antibody fragments and derivatives, all of which specifically bind to a
15 protein of the invention and preferably, a marker protein. In various embodiments, the substantially purified antibodies of the invention, or fragments or derivatives thereof, can be human, non-human, chimeric and/or humanized antibodies. In another aspect, the invention provides non-human antibodies, antibody fragments and derivatives, all of which specifically bind to a protein of the invention and preferably, a marker protein.
20 Such non-human antibodies can be goat, mouse, sheep, horse, chicken, rabbit, or rat antibodies. Alternatively, the non-human antibodies of the invention can be chimeric and/or humanized antibodies. In addition, the non-human antibodies of the invention can be polyclonal antibodies or monoclonal antibodies. In still a further aspect, the invention provides monoclonal antibodies, antibody fragments and derivatives, all of
25 which specifically bind to a protein of the invention and preferably, a marker protein. The monoclonal antibodies can be human, humanized, chimeric and/or non-human antibodies.

The invention also provides a kit containing an antibody of the invention conjugated to a detectable substance, and instructions for use. Still another aspect of the
30 invention is a pharmaceutical composition comprising an antibody of the invention. In one embodiment, the pharmaceutical composition comprises an antibody of the invention and a pharmaceutically acceptable carrier.

III. Recombinant Expression Vectors and Host Cells

Another aspect of the invention pertains to vectors, preferably expression vectors, containing a nucleic acid encoding a marker protein (or a portion of such a protein). As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors, namely expression vectors, are capable of directing the expression of genes to which they are operably linked. In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids (vectors). However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

The recombinant expression vectors of the invention comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell. This means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, which is operably linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner which allows for expression of the nucleotide sequence (*e.g.*, in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host cell). The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel, *Methods in Enzymology: Gene Expression Technology* vol.185, Academic Press, San Diego, CA (1991). Regulatory sequences include those which direct constitutive expression of a nucleotide sequence in many types of host cell and

those which direct expression of the nucleotide sequence only in certain host cells (*e.g.*, tissue-specific regulatory sequences). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, and the like. The expression vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein.

The recombinant expression vectors of the invention can be designed for expression of a marker protein or a segment thereof in prokaryotic (*e.g.*, *E. coli*) or eukaryotic cells (*e.g.*, insect cells {using baculovirus expression vectors}, yeast cells or mammalian cells). Suitable host cells are discussed further in Goeddel, *supra*. Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, for example using T7 promoter regulatory sequences and T7 polymerase.

Expression of proteins in prokaryotes is most often carried out in *E. coli* with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion proteins. Fusion vectors add a number of amino acids to a protein encoded therein, usually to the amino terminus of the recombinant protein. Such fusion vectors typically serve three purposes: 1) to increase expression of recombinant protein; 2) to increase the solubility of the recombinant protein; and 3) to aid in the purification of the recombinant protein by acting as a ligand in affinity purification. Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase. Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc; Smith and Johnson, 1988, *Gene* 67:31-40), pMAL (New England Biolabs, Beverly, MA) and pRIT5 (Pharmacia, Piscataway, NJ) which fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein.

Examples of suitable inducible non-fusion *E. coli* expression vectors include pTrc (Amann *et al.*, 1988, *Gene* 69:301-315) and pET 11d (Studier *et al.*, p. 60-89, In *Gene Expression Technology: Methods in Enzymology* vol.185, Academic Press, San Diego, CA, 1991). Target gene expression from the pTrc vector relies on host RNA

polymerase transcription from a hybrid trp-lac fusion promoter. Target gene expression from the pET 11d vector relies on transcription from a T7 gn10-lac fusion promoter mediated by a co-expressed viral RNA polymerase (T7 gn1). This viral polymerase is supplied by host strains BL21(DE3) or HMS174(DE3) from a resident prophage
5 harboring a T7 gn1 gene under the transcriptional control of the lacUV 5 promoter.

One strategy to maximize recombinant protein expression in *E. coli* is to express the protein in a host bacteria with an impaired capacity to proteolytically cleave the recombinant protein (Gottesman, p. 119-128, In *Gene Expression Technology: Methods in Enzymology* vol. 185, Academic Press, San Diego, CA, 1990. Another
10 strategy is to alter the nucleic acid sequence of the nucleic acid to be inserted into an expression vector so that the individual codons for each amino acid are those preferentially utilized in *E. coli* (Wada *et al.*, 1992, *Nucleic Acids Res.* 20:2111-2118). Such alteration of nucleic acid sequences of the invention can be carried out by standard DNA synthesis techniques.

15 In another embodiment, the expression vector is a yeast expression vector. Examples of vectors for expression in yeast *S. cerevisiae* include pYepSec1 (Baldari *et al.*, 1987, *EMBO J.* 6:229-234), pMFa (Kurjan and Herskowitz, 1982, *Cell* 30:933-943), pJRY88 (Schultz *et al.*, 1987, *Gene* 54:113-123), pYES2 (Invitrogen Corporation, San Diego, CA), and pPicZ (Invitrogen Corp, San Diego, CA).

20 Alternatively, the expression vector is a baculovirus expression vector. Baculovirus vectors available for expression of proteins in cultured insect cells (*e.g.*, Sf 9 cells) include the pAc series (Smith *et al.*, 1983, *Mol. Cell Biol.* 3:2156-2165) and the pVL series (Lucklow and Summers, 1989, *Virology* 170:31-39).

In yet another embodiment, a nucleic acid of the invention is expressed in
25 mammalian cells using a mammalian expression vector. Examples of mammalian expression vectors include pCDM8 (Seed, 1987, *Nature* 329:840) and pMT2PC (Kaufman *et al.*, 1987, *EMBO J.* 6:187-195). When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements. For example, commonly used promoters are derived from polyoma, Adenovirus 2,
30 cytomegalovirus and Simian Virus 40. For other suitable expression systems for both prokaryotic and eukaryotic cells see chapters 16 and 17 of Sambrook *et al.*, *supra*.

In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid preferentially in a particular cell type (*e.g.*, tissue-specific regulatory elements are used to express the nucleic acid). Tissue-specific regulatory elements are known in the art. Non-limiting examples of suitable
5 tissue-specific promoters include the albumin promoter (liver-specific; Pinkert *et al.*, 1987, *Genes Dev.* 1:268-277), lymphoid-specific promoters (Calame and Eaton, 1988, *Adv. Immunol.* 43:235-275), in particular promoters of T cell receptors (Winoto and Baltimore, 1989, *EMBO J.* 8:729-733) and immunoglobulins (Banerji *et al.*, 1983, *Cell* 33:729-740; Queen and Baltimore, 1983, *Cell* 33:741-748), neuron-specific promoters
10 (*e.g.*, the neurofilament promoter; Byrne and Ruddle, 1989, *Proc. Natl. Acad. Sci. USA* 86:5473-5477), pancreas-specific promoters (Edlund *et al.*, 1985, *Science* 230:912-916), and mammary gland-specific promoters (*e.g.*, milk whey promoter; U.S. Patent No. 4,873,316 and European Application Publication No. 264,166). Developmentally-regulated promoters are also encompassed, for example the murine hox promoters
15 (Kessel and Gruss, 1990, *Science* 249:374-379) and the α -fetoprotein promoter (Camper and Tilghman, 1989, *Genes Dev.* 3:537-546).

The invention further provides a recombinant expression vector comprising a DNA molecule of the invention cloned into the expression vector in an antisense orientation. That is, the DNA molecule is operably linked to a regulatory
20 sequence in a manner which allows for expression (by transcription of the DNA molecule) of an RNA molecule which is antisense to the mRNA encoding a polypeptide of the invention. Regulatory sequences operably linked to a nucleic acid cloned in the antisense orientation can be chosen which direct the continuous expression of the antisense RNA molecule in a variety of cell types, for instance viral promoters and/or
25 enhancers, or regulatory sequences can be chosen which direct constitutive, tissue-specific or cell type specific expression of antisense RNA. The antisense expression vector can be in the form of a recombinant plasmid, phagemid, or attenuated virus in which antisense nucleic acids are produced under the control of a high efficiency regulatory region, the activity of which can be determined by the cell type into which the
30 vector is introduced. For a discussion of the regulation of gene expression using antisense genes see Weintraub *et al.*, 1986, *Trends in Genetics*, Vol. 1(1).

Another aspect of the invention pertains to host cells into which a recombinant expression vector of the invention has been introduced. The terms "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but to the progeny or potential
5 progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

A host cell can be any prokaryotic (*e.g.*, *E. coli*) or eukaryotic cell (*e.g.*,
10 insect cells, yeast or mammalian cells).

Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid into a host cell, including calcium
15 phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook, *et al.* (*supra*), and other laboratory manuals.

For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells
20 may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene that encodes a selectable marker (*e.g.*, for resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Preferred selectable markers include those which confer resistance to drugs, such as G418, hygromycin and methotrexate. Cells stably transfected with the introduced nucleic acid
25 can be identified by drug selection (*e.g.*, cells that have incorporated the selectable marker will survive, while the other cells die).

A host cell of the invention, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce a marker protein or a segment thereof. Accordingly, the invention further provides methods for producing a marker protein or a segment
30 thereof using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of the invention (into which a recombinant expression vector encoding a marker protein or a segment thereof has been introduced) in a suitable medium such that the is produced. In another embodiment, the method further

comprises isolating the marker protein or a segment thereof from the medium or the host cell.

The host cells of the invention can also be used to produce nonhuman transgenic animals. For example, in one embodiment, a host cell of the invention is a fertilized oocyte or an embryonic stem cell into which a sequences encoding a marker protein or a segment thereof have been introduced. Such host cells can then be used to create non-human transgenic animals in which exogenous sequences encoding a marker protein of the invention have been introduced into their genome or homologous recombinant animals in which endogenous gene(s) encoding a marker protein have been altered. Such animals are useful for studying the function and/or activity of the marker protein and for identifying and/or evaluating modulators of marker protein. As used herein, a "transgenic animal" is a non-human animal, preferably a mammal, more preferably a rodent such as a rat or mouse, in which one or more of the cells of the animal includes a transgene. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens, amphibians, etc. A transgene is exogenous DNA which is integrated into the genome of a cell from which a transgenic animal develops and which remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, an "homologous recombinant animal" is a non-human animal, preferably a mammal, more preferably a mouse, in which an endogenous gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal, *e.g.*, an embryonic cell of the animal, prior to development of the animal.

A transgenic animal of the invention can be created by introducing a nucleic acid encoding a marker protein into the male pronuclei of a fertilized oocyte, *e.g.*, by microinjection, retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency of expression of the transgene. A tissue-specific regulatory sequence(s) can be operably linked to the transgene to direct expression of the polypeptide of the invention to particular cells. Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, U.S. Patent No.

4,873,191 and in Hogan, *Manipulating the Mouse Embryo*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986. Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of the transgene in its genome and/or expression of mRNA
5 encoding the transgene in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying the transgene can further be bred to other transgenic animals carrying other transgenes.

To create an homologous recombinant animal, a vector is prepared which
10 contains at least a portion of a gene encoding a marker protein into which a deletion, addition or substitution has been introduced to thereby alter, *e.g.*, functionally disrupt, the gene. In a preferred embodiment, the vector is designed such that, upon homologous recombination, the endogenous gene is functionally disrupted (*i.e.*, no longer encodes a functional protein; also referred to as a "knock out" vector). Alternatively, the vector
15 can be designed such that, upon homologous recombination, the endogenous gene is mutated or otherwise altered but still encodes functional protein (*e.g.*, the upstream regulatory region can be altered to thereby alter the expression of the endogenous protein). In the homologous recombination vector, the altered portion of the gene is flanked at its 5' and 3' ends by additional nucleic acid of the gene to allow for
20 homologous recombination to occur between the exogenous gene carried by the vector and an endogenous gene in an embryonic stem cell. The additional flanking nucleic acid sequences are of sufficient length for successful homologous recombination with the endogenous gene. Typically, several kilobases of flanking DNA (both at the 5' and 3' ends) are included in the vector (see, *e.g.*, Thomas and Capecchi, 1987, *Cell* 51:503 for a
25 description of homologous recombination vectors). The vector is introduced into an embryonic stem cell line (*e.g.*, by electroporation) and cells in which the introduced gene has homologously recombined with the endogenous gene are selected (see, *e.g.*, Li *et al.*, 1992, *Cell* 69:915). The selected cells are then injected into a blastocyst of an animal (*e.g.*, a mouse) to form aggregation chimeras (see, *e.g.*, Bradley,
30 *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, Robertson, Ed., IRL, Oxford, 1987, pp. 113-152). A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term. Progeny harboring the homologously recombined DNA in their germ cells can be used to breed

animals in which all cells of the animal contain the homologously recombined DNA by germline transmission of the transgene. Methods for constructing homologous recombination vectors and homologous recombinant animals are described further in Bradley (1991) *Current Opinion in Bio/Technology* 2:823-829 and in PCT Publication
5 NOS. WO 90/11354, WO 91/01140, WO 92/0968, and WO 93/04169.

In another embodiment, transgenic non-human animals can be produced which contain selected systems which allow for regulated expression of the transgene. One example of such a system is the *cre/loxP* recombinase system of bacteriophage P1. For a description of the *cre/loxP* recombinase system, see, e.g., Lakso *et al.* (1992) *Proc.*
10 *Natl. Acad. Sci. USA* 89:6232-6236. Another example of a recombinase system is the FLP recombinase system of *Saccharomyces cerevisiae* (O'Gorman *et al.*, 1991, *Science* 251:1351-1355). If a *cre/loxP* recombinase system is used to regulate expression of the transgene, animals containing transgenes encoding both the *Cre* recombinase and a
selected protein are required. Such animals can be provided through the construction of
15 "double" transgenic animals, e.g., by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase.

Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut *et al.* (1997) *Nature* 385:810-
20 813 and PCT Publication NOS. WO 97/07668 and WO 97/07669.

IV. Pharmaceutical Compositions

The nucleic acid molecules, polypeptides, and antibodies (also referred to herein as "active compounds") of the invention can be incorporated into pharmaceutical
25 compositions suitable for administration. Such compositions typically comprise the nucleic acid molecule, protein, or antibody and a pharmaceutically acceptable carrier. As used herein the language "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical
30 administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is

contemplated. Supplementary active compounds can also be incorporated into the compositions.

The invention includes methods for preparing pharmaceutical compositions for modulating the expression or activity of a marker nucleic acid or protein . Such methods comprise formulating a pharmaceutically acceptable carrier with an agent which modulates expression or activity of a marker nucleic acid or protein. Such compositions can further include additional active agents. Thus, the invention further includes methods for preparing a pharmaceutical composition by formulating a pharmaceutically acceptable carrier with an agent which modulates expression or activity of a marker nucleic acid or protein and one or more additional active compounds.

The invention also provides methods (also referred to herein as "screening assays") for identifying modulators, *i.e.*, candidate or test compounds or agents (*e.g.*, peptides, peptidomimetics, peptoids, small molecules or other drugs) which (a) bind to the marker, or (b) have a modulatory (*e.g.*, stimulatory or inhibitory) effect on the activity of the marker or, more specifically, (c) have a modulatory effect on the interactions of the marker with one or more of its natural substrates (*e.g.*, peptide, protein, hormone, co-factor, or nucleic acid), or (d) have a modulatory effect on the expression of the marker. Such assays typically comprise a reaction between the marker and one or more assay components. The other components may be either the test compound itself, or a combination of test compound and a natural binding partner of the marker.

The test compounds of the present invention may be obtained from any available source, including systematic libraries of natural and/or synthetic compounds. Test compounds may also be obtained by any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; peptoid libraries (libraries of molecules having the functionalities of peptides, but with a novel, non-peptide backbone which are resistant to enzymatic degradation but which nevertheless remain bioactive; see, *e.g.*, Zuckermann *et al.*, 1994, *J. Med. Chem.* 37:2678-85); spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library and peptoid library approaches are limited to peptide libraries, while

the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, 1997, *Anticancer Drug Des.* 12:145).

Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt *et al.* (1993) *Proc. Natl. Acad. Sci. U.S.A.* 90:6909; Erb *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:11422; Zuckermann *et al.* (1994). *J. Med. Chem.* 37:2678; Cho *et al.* (1993) *Science* 261:1303; Carrell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2059; Carell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2061; and in Gallop *et al.* (1994) *J. Med. Chem.* 37:1233.

Libraries of compounds may be presented in solution (*e.g.*, Houghten, 1992, *Biotechniques* 13:412-421), or on beads (Lam, 1991, *Nature* 354:82-84), chips (Fodor, 1993, *Nature* 364:555-556), bacteria and/or spores, (Ladner, USP 5,223,409), plasmids (Cull *et al.*, 1992, *Proc Natl Acad Sci USA* 89:1865-1869) or on phage (Scott and Smith, 1990, *Science* 249:386-390; Devlin, 1990, *Science* 249:404-406; Cwirla *et al.*, 1990, *Proc. Natl. Acad. Sci.* 87:6378-6382; Felici, 1991, *J. Mol. Biol.* 222:301-310; Ladner, *supra.*).

In one embodiment, the invention provides assays for screening candidate or test compounds which are substrates of a protein encoded by or corresponding to a marker or biologically active portion thereof. In another embodiment, the invention provides assays for screening candidate or test compounds which bind to a protein encoded by or corresponding to a marker or biologically active portion thereof. Determining the ability of the test compound to directly bind to a protein can be accomplished, for example, by coupling the compound with a radioisotope or enzymatic label such that binding of the compound to the marker can be determined by detecting the labeled marker compound in a complex. For example, compounds (*e.g.*, marker substrates) can be labeled with ^{125}I , ^{35}S , ^{14}C , or ^3H , either directly or indirectly, and the radioisotope detected by direct counting of radioemission or by scintillation counting. Alternatively, assay components can be enzymatically labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product.

In another embodiment, the invention provides assays for screening candidate or test compounds which modulate the expression of a marker or the activity of a protein encoded by or corresponding to a marker, or a biologically active portion

thereof. In all likelihood, the protein encoded by or corresponding to the marker can, *in vivo*, interact with one or more molecules, such as but not limited to, peptides, proteins, hormones, cofactors and nucleic acids. For the purposes of this discussion, such cellular and extracellular molecules are referred to herein as "binding partners" or marker

5 "substrate".

One necessary embodiment of the invention in order to facilitate such screening is the use of a protein encoded by or corresponding to marker to identify the protein's natural *in vivo* binding partners. There are many ways to accomplish this which are known to one skilled in the art. One example is the use of the marker protein
10 as "bait protein" in a two-hybrid assay or three-hybrid assay (see, *e.g.*, U.S. Patent No. 5,283,317; Zervos *et al*, 1993, *Cell* 72:223-232; Madura *et al*, 1993, *J. Biol. Chem.* 268:12046-12054; Bartel *et al*, 1993, *Biotechniques* 14:920-924; Iwabuchi *et al*, 1993 *Oncogene* 8:1693-1696; Brent WO94/10300) in order to identify other proteins which bind to or interact with the marker (binding partners) and, therefore, are possibly
15 involved in the natural function of the marker. Such marker binding partners are also likely to be involved in the propagation of signals by the marker protein or downstream elements of a marker protein-mediated signaling pathway. Alternatively, such marker protein binding partners may also be found to be inhibitors of the marker protein.

The two-hybrid system is based on the modular nature of most
20 transcription factors, which consist of separable DNA-binding and activation domains. Briefly, the assay utilizes two different DNA constructs. In one construct, the gene that encodes a marker protein fused to a gene encoding the DNA binding domain of a known transcription factor (*e.g.*, GAL-4). In the other construct, a DNA sequence, from a library of DNA sequences, that encodes an unidentified protein ("prey" or "sample") is
25 fused to a gene that codes for the activation domain of the known transcription factor. If the "bait" and the "prey" proteins are able to interact, *in vivo*, forming a marker-dependent complex, the DNA-binding and activation domains of the transcription factor are brought into close proximity. This proximity allows transcription of a reporter gene (*e.g.*, LacZ) which is operably linked to a transcriptional regulatory site responsive to
30 the transcription factor. Expression of the reporter gene can be readily detected and cell colonies containing the functional transcription factor can be isolated and used to obtain the cloned gene which encodes the protein which interacts with the marker protein.

In a further embodiment, assays may be devised through the use of the invention for the purpose of identifying compounds which modulate (*e.g.*, affect either positively or negatively) interactions between a marker protein and its substrates and/or binding partners. Such compounds can include, but are not limited to, molecules such as antibodies, peptides, hormones, oligonucleotides, nucleic acids, and analogs thereof. Such compounds may also be obtained from any available source, including systematic libraries of natural and/or synthetic compounds. The preferred assay components for use in this embodiment is an cervical cancer marker protein identified herein, the known binding partner and/or substrate of same, and the test compound. Test compounds can be supplied from any source.

The basic principle of the assay systems used to identify compounds that interfere with the interaction between the marker protein and its binding partner involves preparing a reaction mixture containing the marker protein and its binding partner under conditions and for a time sufficient to allow the two products to interact and bind, thus forming a complex. In order to test an agent for inhibitory activity, the reaction mixture is prepared in the presence and absence of the test compound. The test compound can be initially included in the reaction mixture, or can be added at a time subsequent to the addition of the marker protein and its binding partner. Control reaction mixtures are incubated without the test compound or with a placebo. The formation of any complexes between the marker protein and its binding partner is then detected. The formation of a complex in the control reaction, but less or no such formation in the reaction mixture containing the test compound, indicates that the compound interferes with the interaction of the marker protein and its binding partner. Conversely, the formation of more complex in the presence of compound than in the control reaction indicates that the compound may enhance interaction of the marker protein and its binding partner.

The assay for compounds that interfere with the interaction of the marker protein with its binding partner may be conducted in a heterogeneous or homogeneous format. Heterogeneous assays involve anchoring either the marker protein or its binding partner onto a solid phase and detecting complexes anchored to the solid phase at the end of the reaction. In homogeneous assays, the entire reaction is carried out in a liquid phase. In either approach, the order of addition of reactants can be varied to obtain different information about the compounds being tested. For example, test compounds

that interfere with the interaction between the marker proteins and the binding partners (e.g., by competition) can be identified by conducting the reaction in the presence of the test substance, *i.e.*, by adding the test substance to the reaction mixture prior to or simultaneously with the marker and its interactive binding partner. Alternatively, test compounds that disrupt preformed complexes, *e.g.*, compounds with higher binding constants that displace one of the components from the complex, can be tested by adding the test compound to the reaction mixture after complexes have been formed. The various formats are briefly described below.

In a heterogeneous assay system, either the marker protein or its binding partner is anchored onto a solid surface or matrix, while the other corresponding non-anchored component may be labeled, either directly or indirectly. In practice, microtitre plates are often utilized for this approach. The anchored species can be immobilized by a number of methods, either non-covalent or covalent, that are typically well known to one who practices the art. Non-covalent attachment can often be accomplished simply by coating the solid surface with a solution of the marker protein or its binding partner and drying. Alternatively, an immobilized antibody specific for the assay component to be anchored can be used for this purpose. Such surfaces can often be prepared in advance and stored.

In related embodiments, a fusion protein can be provided which adds a domain that allows one or both of the assay components to be anchored to a matrix. For example, glutathione-S-transferase/marker fusion proteins or glutathione-S-transferase/binding partner can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtiter plates, which are then combined with the test compound or the test compound and either the non-adsorbed marker or its binding partner, and the mixture incubated under conditions conducive to complex formation (e.g., physiological conditions). Following incubation, the beads or microtiter plate wells are washed to remove any unbound assay components, the immobilized complex assessed either directly or indirectly, for example, as described above. Alternatively, the complexes can be dissociated from the matrix, and the level of marker binding or activity determined using standard techniques.

Other techniques for immobilizing proteins on matrices can also be used in the screening assays of the invention. For example, either a marker protein or a marker protein binding partner can be immobilized utilizing conjugation of biotin and

streptavidin. Biotinylated marker protein or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (*e.g.*, biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). In certain embodiments, the
5 protein-immobilized surfaces can be prepared in advance and stored.

In order to conduct the assay, the corresponding partner of the immobilized assay component is exposed to the coated surface with or without the test compound. After the reaction is complete, unreacted assay components are removed (*e.g.*, by washing) and any complexes formed will remain immobilized on the solid
10 surface. The detection of complexes anchored on the solid surface can be accomplished in a number of ways. Where the non-immobilized component is pre-labeled, the detection of label immobilized on the surface indicates that complexes were formed. Where the non-immobilized component is not pre-labeled, an indirect label can be used to detect complexes anchored on the surface; *e.g.*, using a labeled antibody specific for
15 the initially non-immobilized species (the antibody, in turn, can be directly labeled or indirectly labeled with, *e.g.*, a labeled anti-Ig antibody). Depending upon the order of addition of reaction components, test compounds which modulate (inhibit or enhance) complex formation or which disrupt preformed complexes can be detected.

In an alternate embodiment of the invention, a homogeneous assay may
20 be used. This is typically a reaction, analogous to those mentioned above, which is conducted in a liquid phase in the presence or absence of the test compound. The formed complexes are then separated from unreacted components, and the amount of complex formed is determined. As mentioned for heterogeneous assay systems, the order of addition of reactants to the liquid phase can yield information about which test
25 compounds modulate (inhibit or enhance) complex formation and which disrupt preformed complexes.

In such a homogeneous assay, the reaction products may be separated from unreacted assay components by any of a number of standard techniques, including but not limited to: differential centrifugation, chromatography, electrophoresis and
30 immunoprecipitation. In differential centrifugation, complexes of molecules may be separated from uncomplexed molecules through a series of centrifugal steps, due to the different sedimentation equilibria of complexes based on their different sizes and densities (see, for example, Rivas, G., and Minton, A.P., *Trends Biochem Sci* 1993

Aug;18(8):284-7). Standard chromatographic techniques may also be utilized to separate complexed molecules from uncomplexed ones. For example, gel filtration chromatography separates molecules based on size, and through the utilization of an appropriate gel filtration resin in a column format, for example, the relatively larger
5 complex may be separated from the relatively smaller uncomplexed components. Similarly, the relatively different charge properties of the complex as compared to the uncomplexed molecules may be exploited to differentially separate the complex from the remaining individual reactants, for example through the use of ion-exchange chromatography resins. Such resins and chromatographic techniques are well known to
10 one skilled in the art (see, *e.g.*, Heegaard, 1998, *J Mol. Recognit.* 11:141-148; Hage and Tweed, 1997, *J. Chromatogr. B. Biomed. Sci. Appl.*, 699:499-525). Gel electrophoresis may also be employed to separate complexed molecules from unbound species (see, *e.g.*, Ausubel *et al* (eds.), In: Current Protocols in Molecular Biology, J. Wiley & Sons, New York. 1999). In this technique, protein or nucleic acid complexes are separated based on
15 size or charge, for example. In order to maintain the binding interaction during the electrophoretic process, nondenaturing gels in the absence of reducing agent are typically preferred, but conditions appropriate to the particular interactants will be well known to one skilled in the art. Immunoprecipitation is another common technique utilized for the isolation of a protein-protein complex from solution (see, *e.g.*, Ausubel *et*
20 *al* (eds.), In: Current Protocols in Molecular Biology, J. Wiley & Sons, New York. 1999). In this technique, all proteins binding to an antibody specific to one of the binding molecules are precipitated from solution by conjugating the antibody to a polymer bead that may be readily collected by centrifugation. The bound assay components are released from the beads (through a specific proteolysis event or other
25 technique well known in the art which will not disturb the protein-protein interaction in the complex), and a second immunoprecipitation step is performed, this time utilizing antibodies specific for the correspondingly different interacting assay component. In this manner, only formed complexes should remain attached to the beads. Variations in complex formation in both the presence and the absence of a test compound can be
30 compared, thus offering information about the ability of the compound to modulate interactions between the marker protein and its binding partner.

Also within the scope of the present invention are methods for direct detection of interactions between the marker protein and its natural binding partner and/or a test compound in a homogeneous or heterogeneous assay system without further sample manipulation. For example, the technique of fluorescence energy transfer
5 may be utilized (see, *e.g.*, Lakowicz *et al.*, U.S. Patent No. 5,631,169; Stavrianopoulos *et al.*, U.S. Patent No. 4,868,103). Generally, this technique involves the addition of a fluorophore label on a first 'donor' molecule (*e.g.*, marker or test compound) such that its emitted fluorescent energy will be absorbed by a fluorescent label on a second, 'acceptor' molecule (*e.g.*, marker or test compound), which in turn is able to fluoresce
10 due to the absorbed energy. Alternately, the 'donor' protein molecule may simply utilize the natural fluorescent energy of tryptophan residues. Labels are chosen that emit different wavelengths of light, such that the 'acceptor' molecule label may be differentiated from that of the 'donor'. Since the efficiency of energy transfer between the labels is related to the distance separating the molecules, spatial relationships
15 between the molecules can be assessed. In a situation in which binding occurs between the molecules, the fluorescent emission of the 'acceptor' molecule label in the assay should be maximal. An FET binding event can be conveniently measured through standard fluorometric detection means well known in the art (*e.g.*, using a fluorimeter). A test substance which either enhances or hinders participation of one of the species in
20 the preformed complex will result in the generation of a signal variant to that of background. In this way, test substances that modulate interactions between a marker and its binding partner can be identified in controlled assays.

In another embodiment, modulators of marker expression are identified in a method wherein a cell is contacted with a candidate compound and the expression
25 of marker mRNA or protein in the cell, is determined. The level of expression of marker mRNA or protein in the presence of the candidate compound is compared to the level of expression of marker mRNA or protein in the absence of the candidate compound. The candidate compound can then be identified as a modulator of marker expression based on this comparison. For example, when expression of marker mRNA
30 or protein is greater (statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of marker mRNA or protein expression. Conversely, when expression of marker mRNA or protein is less (statistically significantly less) in the presence of the candidate compound

than in its absence, the candidate compound is identified as an inhibitor of marker mRNA or protein expression. The level of marker mRNA or protein expression in the cells can be determined by methods described herein for detecting marker mRNA or protein.

5 In another aspect, the invention pertains to a combination of two or more of the assays described herein. For example, a modulating agent can be identified using a cell-based or a cell free assay, and the ability of the agent to modulate the activity of a marker protein can be further confirmed *in vivo*, *e.g.*, in a whole animal model for cellular transformation and/or tumorigenesis.

10 This invention further pertains to novel agents identified by the above-described screening assays. Accordingly, it is within the scope of this invention to further use an agent identified as described herein in an appropriate animal model. For example, an agent identified as described herein (*e.g.*, a marker modulating agent, an antisense marker nucleic acid molecule, a marker-specific antibody, or a marker-binding
15 partner) can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as described herein can be used in an animal model to determine the mechanism of action of such an agent. Furthermore, this invention pertains to uses of novel agents identified by the above-described screening assays for treatments as described herein.

20 It is understood that appropriate doses of small molecule agents and protein or polypeptide agents depends upon a number of factors within the knowledge of the ordinarily skilled physician, veterinarian, or researcher. The dose(s) of these agents will vary, for example, depending upon the identity, size, and condition of the subject or sample being treated, further depending upon the route by which the composition is to
25 be administered, if applicable, and the effect which the practitioner desires the agent to have upon the nucleic acid or polypeptide of the invention. Exemplary doses of a small molecule include milligram or microgram amounts per kilogram of subject or sample weight (*e.g.* about 1 microgram per kilogram to about 500 milligrams per kilogram, about 100 micrograms per kilogram to about 5 milligrams per kilogram, or about 1
30 microgram per kilogram to about 50 micrograms per kilogram). Exemplary doses of a protein or polypeptide include gram, milligram or microgram amounts per kilogram of subject or sample weight (*e.g.* about 1 microgram per kilogram to about 5 grams per kilogram, about 100 micrograms per kilogram to about 500 milligrams per kilogram, or

about 1 milligram per kilogram to about 50 milligrams per kilogram). It is furthermore understood that appropriate doses of one of these agents depend upon the potency of the agent with respect to the expression or activity to be modulated. Such appropriate doses can be determined using the assays described herein. When one or more of these agents
5 is to be administered to an animal (*e.g.* a human) in order to modulate expression or activity of a polypeptide or nucleic acid of the invention, a physician, veterinarian, or researcher can, for example, prescribe a relatively low dose at first, subsequently increasing the dose until an appropriate response is obtained. In addition, it is understood that the specific dose level for any particular animal subject will depend
10 upon a variety of factors including the activity of the specific agent employed, the age, body weight, general health, gender, and diet of the subject, the time of administration, the route of administration, the rate of excretion, any drug combination, and the degree of expression or activity to be modulated.

A pharmaceutical composition of the invention is formulated to be
15 compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline
20 solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediamine-tetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with
25 acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the
30 extemporaneous preparation of sterile injectable solutions or dispersions. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL (BASF; Parsippany, NJ) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy

syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound (*e.g.*, a polypeptide or antibody) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium, and then incorporating the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed.

Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches, and the like can contain any of the following ingredients, or compounds of a similar nature: a

binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as
5 peppermint, methyl salicylate, or orange flavoring.

For administration by inhalation, the compounds are delivered in the form of an aerosol spray from a pressurized container or dispenser which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

Systemic administration can also be by transmucosal or transdermal
10 means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal
15 administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

The compounds can also be prepared in the form of suppositories (*e.g.*, with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

20 In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid.
25 Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes having monoclonal antibodies incorporated therein or thereon) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled
30 in the art, for example, as described in U.S. Patent No. 4,522,811.

It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the

subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound
5 and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

For antibodies, the preferred dosage is 0.1 mg/kg to 100 mg/kg of body weight (generally 10 mg/kg to 20 mg/kg). If the antibody is to act in the brain, a dosage of 50 mg/kg to 100 mg/kg is usually appropriate. Generally, partially human antibodies
10 and fully human antibodies have a longer half-life within the human body than other antibodies. Accordingly, lower dosages and less frequent administration is often possible. Modifications such as lipidation can be used to stabilize antibodies and to enhance uptake and tissue penetration (*e.g.*, into the cervical epithelium). A method for lipidation of antibodies is described by Cruikshank *et al.* (1997) *J. Acquired Immune*
15 *Deficiency Syndromes and Human Retrovirology* 14:193.

The invention also provides vaccine compositions for the prevention and/or treatment of cervical cancer. The invention provides cervical cancer vaccine compositions in which a protein of a marker of Table 1, or a combination of proteins of the markers of Table 1, are introduced into a subject in order to stimulate an immune
20 response against the cervical cancer. The invention also provides cervical cancer vaccine compositions in which a gene expression construct, which expresses a marker or fragment of a marker identified in Table 1, is introduced into the subject such that a protein or fragment of a protein encoded by a marker of Table 1 is produced by transfected cells in the subject at a higher than normal level and elicits an immune
25 response.

In one embodiment, a cervical cancer vaccine is provided and employed as an immunotherapeutic agent for the prevention of cervical cancer. In another embodiment, a cervical cancer vaccine is provided and employed as an immunotherapeutic agent for the treatment of cervical cancer.

30 By way of example, a cervical cancer vaccine comprised of the proteins of the markers of Table 1, may be employed for the prevention and/or treatment of cervical cancer in a subject by administering the vaccine by a variety of routes, *e.g.*, intradermally, subcutaneously, or intramuscularly. In addition, the cervical cancer

vaccine can be administered together with adjuvants and/or immunomodulators to boost the activity of the vaccine and the subject's response. In one embodiment, devices and/or compositions containing the vaccine, suitable for sustained or intermittent release could be, implanted in the body or topically applied thereto for the relatively slow
5 release of such materials into the body. The cervical cancer vaccine can be introduced along with immunomodulatory compounds, which can alter the type of immune response produced in order to produce a response which will be more effective in eliminating the cancer.

In another embodiment, a cervical cancer vaccine comprised of an
10 expression construct of the markers of Table 1, may be introduced by injection into muscle or by coating onto microprojectiles and using a device designed for the purpose to fire the projectiles at high speed into the skin. The cells of the subject will then express the protein(s) or fragments of proteins of the markers of Table 1 and induce an immune
15 response. In addition, the cervical cancer vaccine may be introduced along with expression constructs for immunomodulatory molecules, such as cytokines, which may increase the immune response or modulate the type of immune response produced in order to produce a response which will be more effective in eliminating the cancer.

The marker nucleic acid molecules can be inserted into vectors and used
20 as gene therapy vectors. Gene therapy vectors can be delivered to a subject by, for example, intravenous injection, local administration (U.S. Patent 5,328,470), or by stereotactic injection (see, *e.g.*, Chen *et al.*, 1994, *Proc. Natl. Acad. Sci. USA* 91:3054-3057). The pharmaceutical preparation of the gene therapy vector can include the gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which
25 the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells, *e.g.* retroviral vectors, the pharmaceutical preparation can include one or more cells which produce the gene delivery system.

The pharmaceutical compositions can be included in a container, pack, or
30 dispenser together with instructions for administration.

V. Predictive Medicine

The present invention pertains to the field of predictive medicine in which diagnostic assays, prognostic assays, pharmacogenomics, and monitoring clinical trails are used for prognostic (predictive) purposes to thereby treat an individual prophylactically. Accordingly, one aspect of the present invention relates to diagnostic assays for determining the level of expression of one or more marker proteins or nucleic acids, in order to determine whether an individual is at risk of developing cervical cancer. Such assays can be used for prognostic or predictive purposes to thereby prophylactically treat an individual prior to the onset of the cancer.

Yet another aspect of the invention pertains to monitoring the influence of agents (*e.g.*, drugs or other compounds administered either to inhibit cervical cancer or to treat or prevent any other disorder {*i.e.* in order to understand any cervical carcinogenic effects that such treatment may have}) on the expression or activity of a marker of the invention in clinical trials. These and other agents are described in further detail in the following sections.

A. Diagnostic Assays

An exemplary method for detecting the presence or absence of a marker protein or nucleic acid in a biological sample involves obtaining a biological sample (*e.g.* a cervical-associated body fluid) from a test subject and contacting the biological sample with a compound or an agent capable of detecting the polypeptide or nucleic acid (*e.g.*, mRNA, genomic DNA, or cDNA). The detection methods of the invention can thus be used to detect mRNA, protein, cDNA, or genomic DNA, for example, in a biological sample *in vitro* as well as *in vivo*. For example, *in vitro* techniques for detection of mRNA include Northern hybridizations and *in situ* hybridizations. *In vitro* techniques for detection of a marker protein include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence. *In vitro* techniques for detection of genomic DNA include Southern hybridizations. Furthermore, *in vivo* techniques for detection of a marker protein include introducing into a subject a labeled antibody directed against the protein or fragment thereof. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

A general principle of such diagnostic and prognostic assays involves preparing a sample or reaction mixture that may contain a marker, and a probe, under appropriate conditions and for a time sufficient to allow the marker and probe to interact and bind, thus forming a complex that can be removed and/or detected in the reaction mixture. These assays can be conducted in a variety of ways.

For example, one method to conduct such an assay would involve anchoring the marker or probe onto a solid phase support, also referred to as a substrate, and detecting target marker/probe complexes anchored on the solid phase at the end of the reaction. In one embodiment of such a method, a sample from a subject, which is to be assayed for presence and/or concentration of marker, can be anchored onto a carrier or solid phase support. In another embodiment, the reverse situation is possible, in which the probe can be anchored to a solid phase and a sample from a subject can be allowed to react as an unanchored component of the assay.

There are many established methods for anchoring assay components to a solid phase. These include, without limitation, marker or probe molecules which are immobilized through conjugation of biotin and streptavidin. Such biotinylated assay components can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (*e.g.*, biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). In certain embodiments, the surfaces with immobilized assay components can be prepared in advance and stored.

Other suitable carriers or solid phase supports for such assays include any material capable of binding the class of molecule to which the marker or probe belongs. Well-known supports or carriers include, but are not limited to, glass, polystyrene, nylon, polypropylene, nylon, polyethylene, dextran, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite.

In order to conduct assays with the above mentioned approaches, the non-immobilized component is added to the solid phase upon which the second component is anchored. After the reaction is complete, uncomplexed components may be removed (*e.g.*, by washing) under conditions such that any complexes formed will remain immobilized upon the solid phase. The detection of marker/probe complexes anchored to the solid phase can be accomplished in a number of methods outlined herein.

In a preferred embodiment, the probe, when it is the unanchored assay component, can be labeled for the purpose of detection and readout of the assay, either directly or indirectly, with detectable labels discussed herein and which are well-known to one skilled in the art.

5 It is also possible to directly detect marker/probe complex formation without further manipulation or labeling of either component (marker or probe), for example by utilizing the technique of fluorescence energy transfer (see, for example, Lakowicz *et al.*, U.S. Patent No. 5,631,169; Stavrianopoulos, *et al.*, U.S. Patent No. 4,868,103). A fluorophore label on the first, 'donor' molecule is selected such that, upon
10 excitation with incident light of appropriate wavelength, its emitted fluorescent energy will be absorbed by a fluorescent label on a second 'acceptor' molecule, which in turn is able to fluoresce due to the absorbed energy. Alternately, the 'donor' protein molecule may simply utilize the natural fluorescent energy of tryptophan residues. Labels are chosen that emit different wavelengths of light, such that the 'acceptor' molecule label
15 may be differentiated from that of the 'donor'. Since the efficiency of energy transfer between the labels is related to the distance separating the molecules, spatial relationships between the molecules can be assessed. In a situation in which binding occurs between the molecules, the fluorescent emission of the 'acceptor' molecule label in the assay should be maximal. An FET binding event can be conveniently measured
20 through standard fluorometric detection means well known in the art (*e.g.*, using a fluorimeter).

 In another embodiment, determination of the ability of a probe to recognize a marker can be accomplished without labeling either assay component (probe or marker) by utilizing a technology such as real-time Biomolecular Interaction Analysis
25 (BIA) (see, *e.g.*, Sjolander, S. and Urbaniczky, C., 1991, *Anal. Chem.* 63:2338-2345 and Szabo *et al.*, 1995, *Curr. Opin. Struct. Biol.* 5:699-705). As used herein, "BIA" or "surface plasmon resonance" is a technology for studying biospecific interactions in real time, without labeling any of the interactants (*e.g.*, BIAcore). Changes in the mass at the binding surface (indicative of a binding event) result in alterations of the refractive index
30 of light near the surface (the optical phenomenon of surface plasmon resonance (SPR)), resulting in a detectable signal which can be used as an indication of real-time reactions between biological molecules.

Alternatively, in another embodiment, analogous diagnostic and prognostic assays can be conducted with marker and probe as solutes in a liquid phase. In such an assay, the complexed marker and probe are separated from uncomplexed components by any of a number of standard techniques, including but not limited to:

5 differential centrifugation, chromatography, electrophoresis and immunoprecipitation. In differential centrifugation, marker/probe complexes may be separated from uncomplexed assay components through a series of centrifugal steps, due to the different sedimentation equilibria of complexes based on their different sizes and densities (see, for example, Rivas, G., and Minton, A.P., 1993, *Trends Biochem Sci.* 18(8):284-7).

10 Standard chromatographic techniques may also be utilized to separate complexed molecules from uncomplexed ones. For example, gel filtration chromatography separates molecules based on size, and through the utilization of an appropriate gel filtration resin in a column format, for example, the relatively larger complex may be separated from the relatively smaller uncomplexed components. Similarly, the relatively

15 different charge properties of the marker/probe complex as compared to the uncomplexed components may be exploited to differentiate the complex from uncomplexed components, for example through the utilization of ion-exchange chromatography resins. Such resins and chromatographic techniques are well known to one skilled in the art (see, *e.g.*, Heegaard, N.H., 1998, *J. Mol. Recognit.* Winter 11(1-6):141-8; Hage, D.S., and Tweed, S.A. *J Chromatogr B Biomed Sci Appl* 1997 Oct 20 10;699(1-2):499-525). Gel electrophoresis may also be employed to separate complexed assay components from unbound components (see, *e.g.*, Ausubel *et al.*, ed., *Current Protocols in Molecular Biology*, John Wiley & Sons, New York, 1987-1999). In this technique, protein or nucleic acid complexes are separated based on size or charge, for

25 example. In order to maintain the binding interaction during the electrophoretic process, non-denaturing gel matrix materials and conditions in the absence of reducing agent are typically preferred. Appropriate conditions to the particular assay and components thereof will be well known to one skilled in the art.

In a particular embodiment, the level of marker mRNA can be

30 determined both by *in situ* and by *in vitro* formats in a biological sample using methods known in the art. The term "biological sample" is intended to include tissues, cells, biological fluids and isolates thereof, isolated from a subject, as well as tissues, cells and fluids present within a subject. Many expression detection methods use isolated RNA.

For *in vitro* methods, any RNA isolation technique that does not select against the isolation of mRNA can be utilized for the purification of RNA from cervical cells (see, *e.g.*, Ausubel *et al.*, ed., *Current Protocols in Molecular Biology*, John Wiley & Sons, New York 1987-1999). Additionally, large numbers of tissue samples can readily be
5 processed using techniques well known to those of skill in the art, such as, for example, the single-step RNA isolation process of Chomczynski (1989, U.S. Patent No. 4,843,155).

The isolated mRNA can be used in hybridization or amplification assays that include, but are not limited to, Southern or Northern analyses, polymerase chain
10 reaction analyses and probe arrays. One preferred diagnostic method for the detection of mRNA levels involves contacting the isolated mRNA with a nucleic acid molecule (probe) that can hybridize to the mRNA encoded by the gene being detected. The nucleic acid probe can be, for example, a full-length cDNA, or a portion thereof, such as an oligonucleotide of at least 7, 15, 30, 50, 100, 250 or 500 nucleotides in length and
15 sufficient to specifically hybridize under stringent conditions to a mRNA or genomic DNA encoding a marker of the present invention. Other suitable probes for use in the diagnostic assays of the invention are described herein. Hybridization of an mRNA with the probe indicates that the marker in question is being expressed.

In one format, the mRNA is immobilized on a solid surface and contacted
20 with a probe, for example by running the isolated mRNA on an agarose gel and transferring the mRNA from the gel to a membrane, such as nitrocellulose. In an alternative format, the probe(s) are immobilized on a solid surface and the mRNA is contacted with the probe(s), for example, in an Affymetrix gene chip array. A skilled artisan can readily adapt known mRNA detection methods for use in detecting the level
25 of mRNA encoded by the markers of the present invention.

An alternative method for determining the level of mRNA marker in a sample involves the process of nucleic acid amplification, *e.g.*, by rtPCR (the experimental embodiment set forth in Mullis, 1987, U.S. Patent No. 4,683,202), ligase chain reaction (Barany, 1991, *Proc. Natl. Acad. Sci. USA*, 88:189-193), self sustained
30 sequence replication (Guatelli *et al.*, 1990, *Proc. Natl. Acad. Sci. USA* 87:1874-1878), transcriptional amplification system (Kwoh *et al.*, 1989, *Proc. Natl. Acad. Sci. USA* 86:1173-1177), Q-Beta Replicase (Lizardi *et al.*, 1988, *Bio/Technology* 6:1197), rolling circle replication (Lizardi *et al.*, U.S. Patent No. 5,854,033) or any other nucleic acid

amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers. As used herein, amplification primers are defined as being
5 a pair of nucleic acid molecules that can anneal to 5' or 3' regions of a gene (plus and minus strands, respectively, or vice-versa) and contain a short region in between. In general, amplification primers are from about 10 to 30 nucleotides in length and flank a region from about 50 to 200 nucleotides in length. Under appropriate conditions and with appropriate reagents, such primers permit the amplification of a nucleic acid
10 molecule comprising the nucleotide sequence flanked by the primers.

For *in situ* methods, mRNA does not need to be isolated from the cervical cells prior to detection. In such methods, a cell or tissue sample is prepared/processed using known histological methods. The sample is then immobilized on a support, typically a glass slide, and then contacted with a probe that can hybridize to mRNA that
15 encodes the marker.

As an alternative to making determinations based on the absolute expression level of the marker, determinations may be based on the normalized expression level of the marker. Expression levels are normalized by correcting the absolute expression level of a marker by comparing its expression to the expression of a
20 gene that is not a marker, *e.g.*, a housekeeping gene that is constitutively expressed. Suitable genes for normalization include housekeeping genes such as the actin gene, or epithelial cell-specific genes. This normalization allows the comparison of the expression level in one sample, *e.g.*, a patient sample, to another sample, *e.g.*, a non-cervical cancer sample, or between samples from different sources.

Alternatively, the expression level can be provided as a relative
25 expression level. To determine a relative expression level of a marker, the level of expression of the marker is determined for 10 or more samples of normal versus cancer cell isolates, preferably 50 or more samples, prior to the determination of the expression level for the sample in question. The mean expression level of each of the genes assayed
30 in the larger number of samples is determined and this is used as a baseline expression level for the marker. The expression level of the marker determined for the test sample (absolute level of expression) is then divided by the mean expression value obtained for that marker. This provides a relative expression level.

Preferably, the samples used in the baseline determination will be from cervical cancer or from non-cervical cancer cells of cervical tissue. The choice of the cell source is dependent on the use of the relative expression level. Using expression found in normal tissues as a mean expression score aids in validating whether the marker
5 assayed is cervical specific (versus normal cells). In addition, as more data is accumulated, the mean expression value can be revised, providing improved relative expression values based on accumulated data. Expression data from cervical cells provides a means for grading the severity of the cervical cancer state.

In another embodiment of the present invention, a marker protein is
10 detected. A preferred agent for detecting marker protein of the invention is an antibody capable of binding to such a protein or a fragment thereof, preferably an antibody with a detectable label. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment or derivative thereof (*e.g.*, Fab or F(ab')₂) can be used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct
15 labeling of the probe or antibody by coupling (*i.e.*, physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with
20 fluorescently labeled streptavidin.

Proteins from cervical cells can be isolated using techniques that are well known to those of skill in the art. The protein isolation methods employed can, for example, be such as those described in Harlow and Lane (Harlow and Lane, 1988, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring
25 Harbor, New York).

A variety of formats can be employed to determine whether a sample contains a protein that binds to a given antibody. Examples of such formats include, but are not limited to, enzyme immunoassay (EIA), radioimmunoassay (RIA), Western blot analysis and enzyme linked immunoabsorbant assay (ELISA). A skilled artisan can
30 readily adapt known protein/antibody detection methods for use in determining whether cervical cells express a marker of the present invention.

In one format, antibodies, or antibody fragments or derivatives, can be used in methods such as Western blots or immunofluorescence techniques to detect the expressed proteins. In such uses, it is generally preferable to immobilize either the antibody or proteins on a solid support. Suitable solid phase supports or carriers include
5 any support capable of binding an antigen or an antibody. Well-known supports or carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite.

One skilled in the art will know many other suitable carriers for binding antibody or antigen, and will be able to adapt such support for use with the present
10 invention. For example, protein isolated from cervical cells can be run on a polyacrylamide gel electrophoresis and immobilized onto a solid phase support such as nitrocellulose. The support can then be washed with suitable buffers followed by treatment with the detectably labeled antibody. The solid phase support can then be washed with the buffer a second time to remove unbound antibody. The amount of
15 bound label on the solid support can then be detected by conventional means.

The invention also encompasses kits for detecting the presence of a marker protein or nucleic acid in a biological sample (*e.g.*, cervical smear). Such kits can be used to determine if a subject is suffering from or is at increased risk of developing cervical cancer. For example, the kit can comprise a labeled compound or
20 agent capable of detecting a marker protein or nucleic acid in a biological sample and means for determining the amount of the protein or mRNA in the sample (*e.g.*, an antibody which binds the protein or a fragment thereof, or an oligonucleotide probe which binds to DNA or mRNA encoding the protein). Kits can also include instructions for interpreting the results obtained using the kit.

25 For antibody-based kits, the kit can comprise, for example: (1) a first antibody (*e.g.*, attached to a solid support) which binds to a marker protein; and, optionally, (2) a second, different antibody which binds to either the protein or the first antibody and is conjugated to a detectable label.

For oligonucleotide-based kits, the kit can comprise, for example: (1) an
30 oligonucleotide, *e.g.*, a detectably labeled oligonucleotide, which hybridizes to a nucleic acid sequence encoding a marker protein or (2) a pair of primers useful for amplifying a marker nucleic acid molecule. The kit can also comprise, *e.g.*, a buffering agent, a preservative, or a protein stabilizing agent. The kit can further comprise components

necessary for detecting the detectable label (*e.g.*, an enzyme or a substrate). The kit can also contain a control sample or a series of control samples which can be assayed and compared to the test sample. Each component of the kit can be enclosed within an individual container and all of the various containers can be within a single package,
5 along with instructions for interpreting the results of the assays performed using the kit.

B. Pharmacogenomics

The markers of the invention are also useful as pharmacogenomic markers. As used herein, a "pharmacogenomic marker" is an objective biochemical
10 marker whose expression level correlates with a specific clinical drug response or susceptibility in a patient (see, *e.g.*, McLeod *et al.* (1999) *Eur. J. Cancer* 35(12): 1650-1652). The presence or quantity of the pharmacogenomic marker expression is related to the predicted response of the patient and more particularly the patient's tumor to therapy with a specific drug or class of drugs. By assessing the presence or quantity of
15 the expression of one or more pharmacogenomic markers in a patient, a drug therapy which is most appropriate for the patient, or which is predicted to have a greater degree of success, may be selected. For example, based on the presence or quantity of RNA or protein encoded by specific tumor markers in a patient, a drug or course of treatment may be selected that is optimized for the treatment of the specific tumor likely to be
20 present in the patient. The use of pharmacogenomic markers therefore permits selecting or designing the most appropriate treatment for each cancer patient without trying different drugs or regimes.

Another aspect of pharmacogenomics deals with genetic conditions that alters the way the body acts on drugs. These pharmacogenetic conditions can occur
25 either as rare defects or as polymorphisms. For example, glucose-6-phosphate dehydrogenase (G6PD) deficiency is a common inherited enzymopathy in which the main clinical complication is hemolysis after ingestion of oxidant drugs (anti-malarials, sulfonamides, analgesics, nitrofurans) and consumption of fava beans.

As an illustrative embodiment, the activity of drug metabolizing enzymes
30 is a major determinant of both the intensity and duration of drug action. The discovery of genetic polymorphisms of drug metabolizing enzymes (*e.g.*, N-acetyltransferase 2 (NAT 2) and cytochrome P450 enzymes CYP2D6 and CYP2C19) has provided an explanation as to why some patients do not obtain the expected drug effects or show

exaggerated drug response and serious toxicity after taking the standard and safe dose of a drug. These polymorphisms are expressed in two phenotypes in the population, the extensive metabolizer (EM) and poor metabolizer (PM). The prevalence of PM is different among different populations. For example, the gene coding for CYP2D6 is
5 highly polymorphic and several mutations have been identified in PM, which all lead to the absence of functional CYP2D6. Poor metabolizers of CYP2D6 and CYP2C19 quite frequently experience exaggerated drug response and side effects when they receive standard doses. If a metabolite is the active therapeutic moiety, a PM will show no therapeutic response, as demonstrated for the analgesic effect of codeine mediated by its
10 CYP2D6-formed metabolite morphine. The other extreme are the so called ultra-rapid metabolizers who do not respond to standard doses. Recently, the molecular basis of ultra-rapid metabolism has been identified to be due to CYP2D6 gene amplification.

Thus, the level of expression of a marker of the invention in an individual can be determined to thereby select appropriate agent(s) for therapeutic or prophylactic
15 treatment of the individual. In addition, pharmacogenetic studies can be used to apply genotyping of polymorphic alleles encoding drug-metabolizing enzymes to the identification of an individual's drug responsiveness phenotype. This knowledge, when applied to dosing or drug selection, can avoid adverse reactions or therapeutic failure and thus enhance therapeutic or prophylactic efficiency when treating a subject with a
20 modulator of expression of a marker of the invention.

C. Monitoring Clinical Trials

Monitoring the influence of agents (*e.g.*, drug compounds) on the level of expression of a marker of the invention can be applied not only in basic drug screening,
25 but also in clinical trials. For example, the effectiveness of an agent to affect marker expression can be monitored in clinical trials of subjects receiving treatment for cervical cancer. In a preferred embodiment, the present invention provides a method for monitoring the effectiveness of treatment of a subject with an agent (*e.g.*, an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug
30 candidate) comprising the steps of (i) obtaining a pre-administration sample from a subject prior to administration of the agent; (ii) detecting the level of expression of one or more selected markers of the invention in the pre-administration sample; (iii) obtaining one or more post-administration samples from the subject; (iv) detecting the

level of expression of the marker(s) in the post-administration samples; (v) comparing the level of expression of the marker(s) in the pre-administration sample with the level of expression of the marker(s) in the post-administration sample or samples; and (vi) altering the administration of the agent to the subject accordingly. For example,

- 5 increased expression of the marker gene(s) during the course of treatment may indicate ineffective dosage and the desirability of increasing the dosage. Conversely, decreased expression of the marker gene(s) may indicate efficacious treatment and no need to change dosage.

10 D. Electronic Apparatus Readable Media and Arrays

Electronic apparatus readable media comprising a marker of the present invention is also provided. As used herein, "electronic apparatus readable media" refers to any suitable medium for storing, holding or containing data or information that can be read and accessed directly by an electronic apparatus. Such media can include, but are
15 not limited to: magnetic storage media, such as floppy discs, hard disc storage medium, and magnetic tape; optical storage media such as compact disc; electronic storage media such as RAM, ROM, EPROM, EEPROM and the like; general hard disks and hybrids of these categories such as magnetic/optical storage media. The medium is adapted or configured for having recorded thereon a marker of the present invention.

20 As used herein, the term "electronic apparatus" is intended to include any suitable computing or processing apparatus or other device configured or adapted for storing data or information. Examples of electronic apparatus suitable for use with the present invention include stand-alone computing apparatus; networks, including a local area network (LAN), a wide area network (WAN) Internet, Intranet, and Extranet;
25 electronic appliances such as a personal digital assistants (PDAs), cellular phone, pager and the like; and local and distributed processing systems.

As used herein, "recorded" refers to a process for storing or encoding information on the electronic apparatus readable medium. Those skilled in the art can readily adopt any of the presently known methods for recording information on known
30 media to generate manufactures comprising the markers of the present invention.

A variety of software programs and formats can be used to store the marker information of the present invention on the electronic apparatus readable medium. For example, the marker nucleic acid sequence can be represented in a word

processing text file, formatted in commercially-available software such as WordPerfect and MicroSoft Word, or represented in the form of an ASCII file, stored in a database application, such as DB2, Sybase, Oracle, or the like, as well as in other forms. Any number of data processor structuring formats (*e.g.*, text file or database) may be
5 employed in order to obtain or create a medium having recorded thereon the markers of the present invention.

By providing the markers of the invention in readable form, one can routinely access the marker sequence information for a variety of purposes. For example, one skilled in the art can use the nucleotide or amino acid sequences of the
10 present invention in readable form to compare a target sequence or target structural motif with the sequence information stored within the data storage means. Search means are used to identify fragments or regions of the sequences of the invention which match a particular target sequence or target motif.

The present invention therefore provides a medium for holding
15 instructions for performing a method for determining whether a subject has cervical cancer or a pre-disposition to cervical cancer, wherein the method comprises the steps of determining the presence or absence of a marker and based on the presence or absence of the marker, determining whether the subject has cervical cancer or a pre-disposition to cervical cancer and/or recommending a particular treatment for cervical cancer or pre-
20 cervical cancer condition.

The present invention further provides in an electronic system and/or in a network, a method for determining whether a subject has cervical cancer or a pre-disposition to cervical cancer associated with a marker wherein the method comprises the steps of determining the presence or absence of the marker, and based on the
25 presence or absence of the marker, determining whether the subject has cervical cancer or a pre-disposition to cervical cancer, and/or recommending a particular treatment for the cervical cancer or pre-cervical cancer condition. The method may further comprise the step of receiving phenotypic information associated with the subject and/or acquiring from a network phenotypic information associated with the subject.

30 The present invention also provides in a network, a method for determining whether a subject has cervical cancer or a pre-disposition to cervical cancer associated with a marker, said method comprising the steps of receiving information associated with the marker receiving phenotypic information associated with the subject,

acquiring information from the network corresponding to the marker and/or cervical cancer, and based on one or more of the phenotypic information, the marker, and the acquired information, determining whether the subject has a cervical cancer or a pre-disposition to cervical cancer. The method may further comprise the step of
5 recommending a particular treatment for the cervical cancer or pre-cervical cancer condition.

The present invention also provides a business method for determining whether a subject has cervical cancer or a pre-disposition to cervical cancer, said method comprising the steps of receiving information associated with the marker, receiving
10 phenotypic information associated with the subject, acquiring information from the network corresponding to the marker and/or cervical cancer, and based on one or more of the phenotypic information, the marker, and the acquired information, determining whether the subject has cervical cancer or a pre-disposition to cervical cancer. The method may further comprise the step of recommending a particular treatment for the
15 cervical cancer or pre-cervical cancer condition.

The invention also includes an array comprising a marker of the present invention. The array can be used to assay expression of one or more genes in the array. In one embodiment, the array can be used to assay gene expression in a tissue to ascertain tissue specificity of genes in the array. In this manner, up to about 7600 genes
20 can be simultaneously assayed for expression. This allows a profile to be developed showing a battery of genes specifically expressed in one or more tissues.

In addition to such qualitative determination, the invention allows the quantitation of gene expression. Thus, not only tissue specificity, but also the level of expression of a battery of genes in the tissue is ascertainable. Thus, genes can be
25 grouped on the basis of their tissue expression *per se* and level of expression in that tissue. This is useful, for example, in ascertaining the relationship of gene expression between or among tissues. Thus, one tissue can be perturbed and the effect on gene expression in a second tissue can be determined. In this context, the effect of one cell type on another cell type in response to a biological stimulus can be determined. Such a
30 determination is useful, for example, to know the effect of cell-cell interaction at the level of gene expression. If an agent is administered therapeutically to treat one cell type but has an undesirable effect on another cell type, the invention provides an assay to determine the molecular basis of the undesirable effect and thus provides the

opportunity to co-administer a counteracting agent or otherwise treat the undesired effect. Similarly, even within a single cell type, undesirable biological effects can be determined at the molecular level. Thus, the effects of an agent on expression of other than the target gene can be ascertained and counteracted.

5 In another embodiment, the array can be used to monitor the time course of expression of one or more genes in the array. This can occur in various biological contexts, as disclosed herein, for example development of cervical cancer, progression of cervical cancer, and processes, such a cellular transformation associated with cervical cancer.

10 The array is also useful for ascertaining the effect of the expression of a gene on the expression of other genes in the same cell or in different cells. This provides, for example, for a selection of alternate molecular targets for therapeutic intervention if the ultimate or downstream target cannot be regulated.

The array is also useful for ascertaining differential expression patterns of
15 one or more genes in normal and abnormal cells. This provides a battery of genes that could serve as a molecular target for diagnosis or therapeutic intervention.

E. Surrogate Markers

The markers of the invention may serve as surrogate markers for one or
20 more disorders or disease states or for conditions leading up to disease states, and in particular, cervical cancer. As used herein, a "surrogate marker" is an objective biochemical marker which correlates with the absence or presence of a disease or disorder, or with the progression of a disease or disorder (*e.g.*, with the presence or absence of a tumor). The presence or quantity of such markers is independent of the
25 disease. Therefore, these markers may serve to indicate whether a particular course of treatment is effective in lessening a disease state or disorder. Surrogate markers are of particular use when the presence or extent of a disease state or disorder is difficult to assess through standard methodologies (*e.g.*, early stage tumors), or when an assessment of disease progression is desired before a potentially dangerous clinical endpoint is
30 reached (*e.g.*, an assessment of cardiovascular disease may be made using cholesterol levels as a surrogate marker, and an analysis of HIV infection may be made using HIV RNA levels as a surrogate marker, well in advance of the undesirable clinical outcomes of myocardial infarction or fully-developed AIDS). Examples of the use of surrogate

markers in the art include: Koomen *et al.* (2000) *J. Mass. Spectrom.* 35: 258-264; and James (1994) *AIDS Treatment News Archive* 209.

The markers of the invention are also useful as pharmacodynamic markers. As used herein, a “pharmacodynamic marker” is an objective biochemical marker which correlates specifically with drug effects. The presence or quantity of a pharmacodynamic marker is not related to the disease state or disorder for which the drug is being administered; therefore, the presence or quantity of the marker is indicative of the presence or activity of the drug in a subject. For example, a pharmacodynamic marker may be indicative of the concentration of the drug in a biological tissue, in that the marker is either expressed or transcribed or not expressed or transcribed in that tissue in relationship to the level of the drug. In this fashion, the distribution or uptake of the drug may be monitored by the pharmacodynamic marker. Similarly, the presence or quantity of the pharmacodynamic marker may be related to the presence or quantity of the metabolic product of a drug, such that the presence or quantity of the marker is indicative of the relative breakdown rate of the drug *in vivo*. Pharmacodynamic markers are of particular use in increasing the sensitivity of detection of drug effects, particularly when the drug is administered in low doses. Since even a small amount of a drug may be sufficient to activate multiple rounds of marker transcription or expression, the amplified marker may be in a quantity which is more readily detectable than the drug itself. Also, the marker may be more easily detected due to the nature of the marker itself; for example, using the methods described herein, antibodies may be employed in an immune-based detection system for a protein marker, or marker-specific radiolabeled probes may be used to detect a mRNA marker. Furthermore, the use of a pharmacodynamic marker may offer mechanism-based prediction of risk due to drug treatment beyond the range of possible direct observations. Examples of the use of pharmacodynamic markers in the art include: Matsuda *et al.* US 6,033,862; Hattis *et al.* (1991) *Env. Health Perspect.* 90: 229-238; Schentag (1999) *Am. J. Health-Syst. Pharm.* 56 Suppl. 3: S21-S24; and Nicolau (1999) *Am. J. Health-Syst. Pharm.* 56 Suppl. 3: S16-S20.

VI. Experimental Protocol

A. Identification of clones

Cervical tumor specific cDNA clones were identified by transcription profiling using mRNA from 12 cervical tumors, 5 CIN III, 5 CIN I and 12 normal
5 cervical tissues. The subtracted libraries were constructed using mRNA from at least three independent normal ectocervix, B-lymphocytes, T-lymphocytes and other white blood cells (in activated and resting states) as drivers and four independent stage 1B cervical tumors or four independent CIN III cervical samples as testers. The top up-regulated clones in tumors or CIN III cervical tissues, as determined by proprietary
10 statistical analysis methods, were selected. The clusters in which the selected clones belong were blasted against both public and proprietary sequence databases in order to identify other EST sequences or clusters with significant overlap. Thus, contiguous EST sequences and/or clusters were assembled into full-length genes.

An identification of protein sequence corresponding to the clone was
15 accomplished by obtaining one of the following:

- a) a direct match between the protein sequence and at least one EST sequence in one of its 6 possible translations;
- b) a direct match between the nucleotide sequence for the mRNA corresponding to the protein sequence and at least one EST sequence;
- 20 c) a match between the protein sequence and a contiguous assembly (contig) of the EST sequences with other available EST sequences in the databases in one of its 6 possible translations; or
- d) a match between the nucleotide sequence for the mRNA corresponding to the protein sequence and a contiguous assembly of the EST sequences with other
25 available EST sequences in the databases in one of its 6 possible translations.

VII. Summary of the Data

Tables 1-3 list the markers obtained using the foregoing protocol. The tables provide the name of the gene corresponding to the marker ("Gene Name"), the
30 sequence listing identifier of the cDNA sequence of a nucleotide transcript encoded by or corresponding to the marker ("SEQ ID NO (nts)"), the sequence listing identifier of the amino acid sequence of a protein encoded by the nucleotide transcript ("SEQ ID NO

(AAs)'), and the location of the protein coding sequence within the cDNA sequence ("CDS").

Table 1 lists all of the markers of the invention which are over-expressed in cervical cancer cells compared to normal (*i.e.*, non-cancerous) cervical cells. Table 2
5 lists newly-identified nucleotide and amino acid sequences useful as cervical cancer markers. Table 3 lists newly-identified nucleotide sequences useful as cervical cancer markers.

Other Embodiments

10 Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims:

What is claimed:

1. An isolated nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, 143, 145, 147, 149, 151,
5 167, 203, 217, 231, 233, 51, 65, 67, 68, 100, and 153.
2. A vector which contains the nucleic acid molecule of claim 1.
3. A host cell which contains the nucleic acid molecule of claim 1.
- 10 4. A method of assessing whether a patient is afflicted with cervical cancer, the method comprising comparing:
 - a) the level of expression of a marker in a patient sample, wherein the marker is selected from Table 1; and
 - 15 b) the normal level of expression of the marker in a control non-cervical cancer sample,
wherein a significant increase in the level of expression of the marker in the patient sample and the normal level is an indication that the patient is afflicted with cervical cancer.
- 20 5. An isolated polypeptide which is encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, 143, 145, 147, 149, 151, 167, 203, 217, 231, and 233.
- 25 6. An antibody which selectively binds to the polypeptide of claim 5.
7. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, 8, 144, 146, 148, 150, 152, 168, 204, 218, 232, and 234.
- 30 8. An antibody which selectively binds to the polypeptide of claim 7.

SEQUENCE LISTING

<110> Millennium Pharmaceuticals, Inc. et al.

<120> NOVEL GENES, COMPOSITIONS, KITS, AND METHODS FOR
IDENTIFICATION, ASSESSMENT, PREVENTION, AND THERAPY
OF CERVICAL CANCER

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<151> 2001-06-13

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Glu Ser Asp Ala Gln Arg Thr Met Tyr Pro Gly Ser Cys Val Lys Lys						
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Glu Thr Asn Ile Val Lys Leu Leu Glu Lys Gln Tyr Gln Glu Gln Leu						
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Ser Ser Lys Gln Ala His Ala Val Cys Gln Gln Glu Gln His Tyr Phe						
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Asn Glu Met Lys Leu Ser Gln Asp Gln Ile Gly Phe Gln Thr Phe Glu						
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Thr Val Asp Val Lys Phe Lys Glu Glu Phe Lys Pro Leu Ser Lys Glu						
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Leu Gly Glu His Gly Lys Glu Ile Leu Leu Ser Asn Ser Asp Pro His						
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Asp Ile Pro Glu Ser Lys Asp Cys Val Leu Thr Ile Ser Glu Glu Met						
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Gln Leu Ser Leu Ala Gly Arg Glu Lys Leu Cys Cys Glu Leu Arg Asn						
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Pro Pro Glu Ile Leu Ser Asn Glu Arg Tyr Ala Leu Gln Lys Ala Asn						
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Asn Arg Leu Leu Lys Ile Leu Leu Glu Val Val Lys Thr Thr Ala Ala						
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Val Glu Glu Thr Ile Gly Arg His Val Leu Gly Ile Leu Asp Arg Ser						
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Ser Lys Ser Gln Ser Ser Ala Ser Leu Ile Trp Arg Ser Glu Ala Glu						
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Ala Ser Val Lys Ser Cys Val His Glu Glu His Thr Arg Val Thr Asp						
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Glu Ser Ile Pro Ser Tyr Ser Gly Ser Asp Met Pro Arg Asn Asp Ile						
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Asn Met Trp Ser Lys Val Thr Glu Glu Gly Thr Glu Leu Ser Gln Arg						
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Ile	Gln	Glu	Glu	Arg	Glu	Leu	Leu	Ser	Arg	Gln	Lys	Glu	Ala	Met	Lys	
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Asp	Asp	Leu	Gln	Lys	Gln	Val	Lys	Ala	Leu	Glu	Ile	Asp	Val	Glu	Glu	
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Leu Glu Val Val Leu Thr Glu Asp Ala Leu Lys Ser Leu Glu Asn Gln		2460
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Gln	Leu	Glu	Asp	Leu	Val	Glu	Glu	Leu	Ser	Phe	Ser	Arg	Glu	Gln	Ile
530						535					540				
Gln	Arg	Ala	Arg	Gln	Thr	Ile	Ala	Glu	Gln	Glu	Ser	Lys	Leu	Asn	Glu
545					550					555					560
Ala	His	Lys	Ser	Leu	Ser	Thr	Val	Glu	Asp	Leu	Lys	Ala	Glu	Ile	Val
				565					570					575	
Ser	Ala	Ser	Glu	Ser	Arg	Lys	Glu	Leu	Glu	Leu	Lys	His	Glu	Ala	Glu
			580					585					590		
Val	Thr	Asn	Tyr	Lys	Ile	Lys	Leu	Glu	Met	Leu	Glu	Lys	Glu	Lys	Asn
		595				600					605				
Ala	Val	Leu	Asp	Arg	Met	Ala	Glu	Ser	Gln	Glu	Ala	Glu	Leu	Glu	Arg
610						615					620				
Leu	Arg	Thr	Gln	Leu	Leu	Phe	Ser	His	Glu	Glu	Glu	Leu	Ser	Lys	Leu
625					630					635					640
Lys	Glu	Asp	Leu	Glu	Ile	Glu	His	Arg	Ile	Asn	Ile	Glu	Lys	Leu	Lys
			645						650					655	
Asp	Asn	Leu	Gly	Ile	His	Tyr	Lys	Gln	Gln	Ile	Asp	Gly	Leu	Gln	Asn
			660					665					670		
Glu	Met	Ser	Gln	Lys	Ile	Glu	Thr	Met	Gln	Phe	Glu	Lys	Asp	Asn	Leu
		675					680					685			
Ile	Thr	Lys	Gln	Asn	Gln	Leu	Ile	Leu	Glu	Ile	Ser	Lys	Leu	Lys	Asp
690						695					700				
Leu	Gln	Gln	Ser	Leu	Val	Asn	Ser	Lys	Ser	Glu	Glu	Met	Thr	Leu	Gln
705					710						715				720
Ile	Asn	Glu	Leu	Gln	Lys	Glu	Ile	Glu	Ile	Leu	Arg	Gln	Glu	Glu	Lys
			725						730					735	
Glu	Lys	Gly	Thr	Leu	Glu	Gln	Glu	Val	Gln	Glu	Leu	Gln	Leu	Lys	Thr
			740					745					750		
Glu	Leu	Leu	Glu	Lys	Gln	Met	Lys	Glu	Lys	Glu	Asn	Asp	Leu	Gln	Glu
		755					760					765			
Lys	Phe	Ala	Gln	Leu	Glu	Ala	Glu	Asn	Ser	Ile	Leu	Lys	Asp	Glu	Lys
770						775					780				
Lys	Thr	Leu	Glu	Asp	Met	Leu	Lys	Ile	His	Thr	Pro	Val	Ser	Gln	Glu
785					790					795					800
Glu	Arg	Leu	Ile	Phe	Leu	Asp	Ser	Ile	Lys	Ser	Lys	Ser	Lys	Asp	Ser
				805					810					815	
Val	Trp	Glu	Lys	Glu	Ile	Glu	Ile	Leu	Ile	Glu	Glu	Asn	Glu	Asp	Leu
			820					825					830		
Lys	Gln	Gln	Cys	Ile	Gln	Leu	Asn	Glu	Glu	Ile	Glu	Lys	Gln	Arg	Asn

		835					840				845				
Thr	Phe	Ser	Phe	Ala	Glu	Lys	Asn	Phe	Glu	Val	Asn	Tyr	Gln	Glu	Leu
	850					855					860				
Gln	Glu	Glu	Tyr	Ala	Cys	Leu	Leu	Lys	Val	Lys	Asp	Asp	Leu	Glu	Asp
865					870					875					880
Ser	Lys	Asn	Lys	Gln	Glu	Leu	Glu	Tyr	Lys	Ser	Lys	Leu	Lys	Ala	Leu
				885					890					895	
Asn	Glu	Glu	Leu	His	Leu	Gln	Arg	Ile	Asn	Pro	Thr	Thr	Val	Lys	Met
			900					905					910		
Lys	Ser	Ser	Val	Phe	Asp	Glu	Asp	Lys	Thr	Phe	Val	Ala	Glu	Thr	Leu
		915				920						925			
Glu	Met	Gly	Glu	Val	Val	Glu	Lys	Asp	Thr	Thr	Glu	Leu	Met	Glu	Lys
	930					935					940				
Leu	Glu	Val	Thr	Lys	Arg	Glu	Lys	Leu	Glu	Leu	Ser	Gln	Arg	Leu	Ser
945					950					955					960
Asp	Leu	Ser	Glu	Gln	Leu	Lys	Gln	Lys	His	Gly	Glu	Ile	Ser	Phe	Leu
				965					970					975	
Asn	Glu	Glu	Val	Lys	Ser	Leu	Lys	Gln	Glu	Lys	Glu	Gln	Val	Ser	Leu
			980					985					990		
Arg	Cys	Arg	Glu	Leu	Glu	Ile	Ile	Ile	Asn	His	Asn	Arg	Ala	Glu	Asn
		995				1000						1005			
Val	Gln	Ser	Cys	Asp	Thr	Gln	Val	Ser	Ser	Leu	Leu	Asp	Gly	Val	Val
	1010					1015					1020				
Thr	Met	Thr	Ser	Arg	Gly	Ala	Glu	Gly	Ser	Val	Ser	Lys	Val	Asn	Lys
1025					1030					1035					1040
Ser	Phe	Gly	Glu	Glu	Ser	Lys	Ile	Met	Val	Glu	Asp	Lys	Val	Ser	Phe
				1045					1050					1055	
Glu	Asn	Met	Thr	Val	Gly	Glu	Glu	Ser	Lys	Gln	Glu	Gln	Leu	Ile	Leu
			1060					1065					1070		
Asp	His	Leu	Pro	Ser	Val	Thr	Lys	Glu	Ser	Ser	Leu	Arg	Ala	Thr	Gln
		1075					1080					1085			
Pro	Ser	Glu	Asn	Asp	Lys	Leu	Gln	Lys	Glu	Leu	Asn	Val	Leu	Lys	Ser
	1090					1095					1100				
Glu	Gln	Asn	Asp	Leu	Arg	Leu	Gln	Met	Glu	Ala	Gln	Arg	Ile	Cys	Leu
1105					1110					1115					1120
Ser	Leu	Val	Tyr	Ser	Thr	His	Val	Asp	Gln	Val	Arg	Glu	Tyr	Met	Glu
				1125					1130					1135	
Asn	Glu	Lys	Asp	Lys	Ala	Leu	Cys	Ser	Leu	Lys	Glu	Glu	Leu	Ile	Phe
			1140					1145					1150		
Ala	Gln	Glu	Glu	Lys	Ile	Lys	Glu	Leu	Gln	Lys	Ile	His	Gln	Leu	Glu
		1155					1160					1165			
Leu	Gln	Thr	Met	Lys	Thr	Gln	Glu	Thr	Gly	Asp	Glu	Gly	Lys	Pro	Leu
	1170					1175					1180				
His	Leu	Leu	Ile	Gly	Lys	Leu	Gln	Lys	Ala	Val	Ser	Glu	Glu	Cys	Ser
1185					1190					1195					1200
Tyr	Phe	Leu	Gln	Thr	Leu	Cys	Ser	Val	Leu	Gly	Glu	Tyr	Tyr	Thr	Pro
				1205					1210					1215	
Ala	Leu	Lys	Cys	Glu	Val	Asn	Ala	Glu	Asp	Lys	Glu	Asn	Ser	Gly	Asp
			1220					1225					1230		
Tyr	Ile	Ser	Glu	Asn	Glu	Asp	Pro	Glu	Leu	Gln	Asp	Tyr	Arg	Tyr	Glu
		1235					1240					1245			
Val	Gln	Asp	Phe	Gln	Glu	Asn	Met	His	Thr	Leu	Leu	Asn	Lys	Val	Thr
	1250					1255					1260				
Glu	Glu	Tyr	Asn	Lys	Leu	Leu	Val	Leu	Gln	Thr	Arg	Leu	Ser	Lys	Ile
1265					1270					1275					1280
Trp	Gly	Gln	Gln	Thr	Asp	Gly	Met	Lys	Leu	Glu	Phe	Gly	Glu	Glu	Asn
				1285					1290					1295	
Leu	Pro	Lys	Glu	Glu	Thr	Glu	Phe	Leu	Ser	Ile	His	Ser	Gln	Met	Thr
			1300					1305					1310		

Asn	Leu	Glu	Asp	Ile	Asp	Val	Asn	His	Lys	Ser	Lys	Leu	Ser	Ser	Leu	1315	1320	1325
Gln	Asp	Leu	Glu	Lys	Thr	Lys	Leu	Glu	Glu	Gln	Val	Gln	Glu	Leu	Glu	1330	1335	1340
Ser	Leu	Ile	Ser	Ser	Leu	Gln	Gln	Gln	Leu	Lys	Glu	Thr	Glu	Gln	Asn	1345	1350	1355
Tyr	Glu	Ala	Glu	Ile	His	Cys	Leu	Gln	Lys	Arg	Leu	Gln	Ala	Val	Ser	1365	1370	1375
Glu	Ser	Thr	Val	Pro	Pro	Ser	Leu	Pro	Val	Asp	Ser	Val	Val	Ile	Thr	1380	1385	1390
Glu	Ser	Asp	Ala	Gln	Arg	Thr	Met	Tyr	Pro	Gly	Ser	Cys	Val	Lys	Lys	1395	1400	1405
Asn	Ile	Asp	Gly	Thr	Ile	Glu	Phe	Ser	Gly	Glu	Phe	Gly	Val	Lys	Glu	1410	1415	1420
Glu	Thr	Asn	Ile	Val	Lys	Leu	Leu	Glu	Lys	Gln	Tyr	Gln	Glu	Gln	Leu	1425	1430	1435
Glu	Glu	Glu	Val	Ala	Lys	Val	Ile	Val	Ser	Met	Ser	Ile	Ala	Phe	Ala	1445	1450	1455
Gln	Gln	Thr	Glu	Leu	Ser	Arg	Ile	Ser	Gly	Gly	Lys	Glu	Asn	Thr	Ala	1460	1465	1470
Ser	Ser	Lys	Gln	Ala	His	Ala	Val	Cys	Gln	Gln	Glu	Gln	His	Tyr	Phe	1475	1480	1485
Asn	Glu	Met	Lys	Leu	Ser	Gln	Asp	Gln	Ile	Gly	Phe	Gln	Thr	Phe	Glu	1490	1495	1500
Thr	Val	Asp	Val	Lys	Phe	Lys	Glu	Glu	Phe	Lys	Pro	Leu	Ser	Lys	Glu	1505	1510	1515
Leu	Gly	Glu	His	Gly	Lys	Glu	Ile	Leu	Leu	Ser	Asn	Ser	Asp	Pro	His	1525	1530	1535
Asp	Ile	Pro	Glu	Ser	Lys	Asp	Cys	Val	Leu	Thr	Ile	Ser	Glu	Glu	Met	1540	1545	1550
Phe	Ser	Lys	Asp	Lys	Thr	Phe	Ile	Val	Arg	Gln	Ser	Ile	His	Asp	Glu	1555	1560	1565
Ile	Ser	Val	Ser	Ser	Met	Asp	Ala	Ser	Arg	Gln	Leu	Met	Leu	Asn	Glu	1570	1575	1580
Glu	Gln	Leu	Glu	Asp	Met	Arg	Gln	Glu	Leu	Val	Arg	Gln	Tyr	Gln	Glu	1585	1590	1595
His	Gln	Gln	Ala	Thr	Glu	Leu	Leu	Arg	Gln	Ala	His	Met	Arg	Gln	Met	1605	1610	1615
Glu	Arg	Gln	Arg	Glu	Asp	Gln	Glu	Gln	Leu	Gln	Glu	Glu	Ile	Lys	Arg	1620	1625	1630
Leu	Asn	Arg	Gln	Leu	Ala	Gln	Arg	Ser	Ser	Ile	Asp	Asn	Glu	Asn	Leu	1635	1640	1645
Val	Ser	Glu	Arg	Glu	Arg	Val	Leu	Leu	Glu	Glu	Leu	Glu	Ala	Leu	Lys	1650	1655	1660
Gln	Leu	Ser	Leu	Ala	Gly	Arg	Glu	Lys	Leu	Cys	Cys	Glu	Leu	Arg	Asn	1665	1670	1675
Ser	Ser	Thr	Gln	Thr	Gln	Asn	Gly	Asn	Glu	Asn	Gln	Gly	Glu	Val	Glu	1685	1690	1695
Glu	Gln	Thr	Phe	Lys	Glu	Lys	Glu	Leu	Asp	Arg	Lys	Pro	Glu	Asp	Val	1700	1705	1710
Pro	Pro	Glu	Ile	Leu	Ser	Asn	Glu	Arg	Tyr	Ala	Leu	Gln	Lys	Ala	Asn	1715	1720	1725
Asn	Arg	Leu	Leu	Lys	Ile	Leu	Leu	Glu	Val	Val	Lys	Thr	Thr	Ala	Ala	1730	1735	1740
Val	Glu	Glu	Thr	Ile	Gly	Arg	His	Val	Leu	Gly	Ile	Leu	Asp	Arg	Ser	1745	1750	1755
Ser	Lys	Ser	Gln	Ser	Ser	Ala	Ser	Leu	Ile	Trp	Arg	Ser	Glu	Ala	Glu	1765	1770	1775
Ala	Ser	Val	Lys	Ser	Cys	Val	His	Glu	Glu	His	Thr	Arg	Val	Thr	Asp			

1780					1785					1790						
Glu	Ser	Ile	Pro	Ser	Tyr	Ser	Gly	Ser	Asp	Met	Pro	Arg	Asn	Asp	Ile	
1795					1800					1805						
Asn	Met	Trp	Ser	Lys	Val	Thr	Glu	Glu	Gly	Thr	Glu	Leu	Ser	Gln	Arg	
1810					1815					1820						
Leu	Val	Arg	Ser	Gly	Phe	Ala	Gly	Thr	Glu	Ile	Asp	Pro	Glu	Asn	Glu	
1825					1830					1835					1840	
Glu	Leu	Met	Leu	Asn	Ile	Ser	Ser	Arg	Leu	Gln	Ala	Ala	Val	Glu	Lys	
1845					1850					1855						
Leu	Leu	Glu	Ala	Ile	Ser	Glu	Thr	Ser	Ser	Gln	Leu	Glu	His	Ala	Lys	
1860					1865					1870						
Val	Thr	Gln	Thr	Glu	Leu	Met	Arg	Glu	Ser	Phe	Arg	Gln	Lys	Gln	Glu	
1875					1880					1885						
Ala	Thr	Glu	Ser	Leu	Lys	Cys	Gln	Glu	Glu	Leu	Arg	Glu	Arg	Leu	His	
1890					1895					1900						
Glu	Glu	Ser	Arg	Ala	Arg	Glu	Gln	Leu	Ala	Val	Glu	Leu	Ser	Lys	Ala	
1905					1910					1915					1920	
Glu	Gly	Val	Ile	Asp	Gly	Tyr	Ala	Asp	Glu	Lys	Thr	Leu	Phe	Glu	Arg	
1925					1930					1935						
Gln	Ile	Gln	Glu	Lys	Thr	Asp	Ile	Ile	Asp	Arg	Leu	Glu	Gln	Glu	Leu	
1940					1945					1950						
Leu	Cys	Ala	Ser	Asn	Arg	Leu	Gln	Glu	Leu	Glu	Ala	Glu	Gln	Gln	Gln	
1955					1960					1965						
Ile	Gln	Glu	Glu	Arg	Glu	Leu	Leu	Ser	Arg	Gln	Lys	Glu	Ala	Met	Lys	
1970					1975					1980						
Ala	Glu	Ala	Gly	Pro	Val	Glu	Gln	Gln	Leu	Leu	Gln	Glu	Thr	Glu	Lys	
1985					1990					1995					2000	
Leu	Met	Lys	Glu	Lys	Leu	Glu	Val	Gln	Cys	Gln	Ala	Glu	Lys	Val	Arg	
2005					2010					2015						
Asp	Asp	Leu	Gln	Lys	Gln	Val	Lys	Ala	Leu	Glu	Ile	Asp	Val	Glu	Glu	
2020					2025					2030						
Gln	Val	Ser	Arg	Phe	Ile	Glu	Leu	Glu	Gln	Glu	Lys	Asn	Thr	Glu	Leu	
2035					2040					2045						
Met	Asp	Leu	Arg	Gln	Gln	Asn	Gln	Ala	Leu	Glu	Lys	Gln	Leu	Glu	Lys	
2050					2055					2060						
Met	Arg	Lys	Phe	Leu	Asp	Glu	Gln	Ala	Ile	Asp	Arg	Glu	His	Glu	Arg	
2065					2070					2075					2080	
Asp	Val	Phe	Gln	Gln	Glu	Ile	Gln	Lys	Leu	Glu	Gln	Gln	Leu	Lys	Val	
2085					2090					2095						
Val	Pro	Arg	Phe	Gln	Pro	Ile	Ser	Glu	His	Gln	Thr	Arg	Glu	Val	Glu	
2100					2105					2110						
Gln	Leu	Ala	Asn	His	Leu	Lys	Glu	Lys	Thr	Asp	Lys	Cys	Ser	Glu	Leu	
2115					2120					2125						
Leu	Leu	Ser	Lys	Glu	Gln	Leu	Gln	Arg	Asp	Ile	Gln	Glu	Arg	Asn	Glu	
2130					2135					2140						
Glu	Ile	Glu	Lys	Leu	Glu	Phe	Arg	Val	Arg	Glu	Leu	Glu	Gln	Ala	Leu	
2145					2150					2155					2160	
Leu	Val	Glu	Asp	Arg	Lys	His	Phe	Gly	Ala	Val	Glu	Ala	Lys	Pro	Glu	
2165					2170					2175						
Leu	Ser	Leu	Glu	Val	Gln	Leu	Gln	Ala	Glu	Arg	Asp	Ala	Ile	Asp	Arg	
2180					2185					2190						
Lys	Glu	Lys	Glu	Ile	Thr	Asn	Leu	Glu	Glu	Gln	Leu	Glu	Gln	Phe	Arg	
2195					2200					2205						
Glu	Glu	Leu	Glu	Asn	Lys	Asn	Glu	Glu	Val	Gln	Gln	Leu	His	Met	Gln	
2210					2215					2220						
Leu	Glu	Ile	Gln	Lys	Lys	Glu	Ser	Thr	Thr	Arg	Leu	Gln	Glu	Leu	Glu	
2225					2230					2235					2240	
Gln	Glu	Asn	Lys	Leu	Phe	Lys	Asp	Asp	Met	Glu	Lys	Leu	Gly	Leu	Ala	
2245					2250					2255						

Ile	Lys	Glu	Ser	Asp	Ala	Met	Ser	Thr	Gln	Asp	Gln	His	Val	Leu	Phe	2260	2265	2270
Gly	Lys	Phe	Ala	Gln	Ile	Ile	Gln	Glu	Lys	Glu	Val	Glu	Ile	Asp	Gln	2275	2280	2285
Leu	Asn	Glu	Gln	Val	Thr	Lys	Leu	Gln	Gln	Gln	Leu	Lys	Ile	Thr	Thr	2290	2295	2300
Asp	Asn	Lys	Val	Ile	Glu	Glu	Lys	Asn	Glu	Leu	Ile	Arg	Asp	Leu	Glu	2305	2310	2315
Thr	Gln	Ile	Glu	Cys	Leu	Met	Ser	Asp	Gln	Glu	Cys	Val	Lys	Arg	Asn	2325	2330	2335
Arg	Glu	Glu	Glu	Ile	Glu	Gln	Leu	Asn	Glu	Val	Ile	Glu	Lys	Leu	Gln	2340	2345	2350
Gln	Glu	Leu	Ala	Asn	Ile	Gly	Gln	Lys	Thr	Ser	Met	Asn	Ala	His	Ser	2355	2360	2365
Leu	Ser	Glu	Glu	Ala	Asp	Ser	Leu	Lys	His	Gln	Leu	Asp	Val	Val	Ile	2370	2375	2380
Ala	Glu	Lys	Leu	Ala	Leu	Glu	Gln	Gln	Val	Glu	Thr	Ala	Asn	Glu	Glu	2385	2390	2395
Met	Thr	Phe	Met	Lys	Asn	Val	Leu	Lys	Glu	Thr	Asn	Phe	Lys	Met	Asn	2405	2410	2415
Gln	Leu	Thr	Gln	Glu	Leu	Phe	Ser	Leu	Lys	Arg	Glu	Arg	Glu	Ser	Val	2420	2425	2430
Glu	Lys	Ile	Gln	Ser	Ile	Pro	Glu	Asn	Ser	Val	Asn	Val	Ala	Ile	Asp	2435	2440	2445
His	Leu	Ser	Lys	Asp	Lys	Pro	Glu	Leu	Glu	Val	Val	Leu	Thr	Glu	Asp	2450	2455	2460
Ala	Leu	Lys	Ser	Leu	Glu	Asn	Gln	Thr	Tyr	Phe	Lys	Ser	Phe	Glu	Glu	2465	2470	2475
Asn	Gly	Lys	Gly	Ser	Ile	Ile	Asn	Leu	Glu	Thr	Arg	Leu	Leu	Gln	Leu	2485	2490	2495
Glu	Ser	Thr	Val	Ser	Ala	Lys	Asp	Leu	Glu	Leu	Thr	Gln	Cys	Tyr	Lys	2500	2505	2510
Gln	Ile	Lys	Asp	Met	Gln	Glu	Gln	Gly	Gln	Phe	Glu	Thr	Glu	Met	Leu	2515	2520	2525
Gln	Lys	Lys	Ile	Val	Asn	Leu	Gln	Lys	Ile	Val	Glu	Glu	Lys	Val	Ala	2530	2535	2540
Ala	Ala	Leu	Val	Ser	Gln	Ile	Gln	Leu	Glu	Ala	Val	Gln	Glu	Tyr	Ala	2545	2550	2555
Lys	Phe	Cys	Gln	Asp	Asn	Gln	Thr	Ile	Ser	Ser	Glu	Pro	Glu	Arg	Thr	2565	2570	2575
Asn	Ile	Gln	Asn	Leu	Asn	Gln	Leu	Arg	Glu	Asp	Glu	Leu	Gly	Ser	Asp	2580	2585	2590
Ile	Ser	Ala	Leu	Thr	Leu	Arg	Ile	Ser	Glu	Leu	Glu	Ser	Gln	Val	Val	2595	2600	2605
Glu	Met	His	Thr	Ser	Leu	Ile	Leu	Glu	Lys	Glu	Gln	Val	Glu	Ile	Ala	2610	2615	2620
Glu	Lys	Asn	Val	Leu	Glu	Lys	Glu	Lys	Lys	Leu	Leu	Glu	Leu	Gln	Lys	2625	2630	2635
Leu	Leu	Glu	Gly	Asn	Glu	Lys	Lys	Gln	Arg	Glu	Lys	Glu	Lys	Lys	Arg	2645	2650	2655
Ser	Pro	Gln	Asp	Val	Glu	Val	Leu	Lys	Thr	Thr	Thr	Glu	Leu	Phe	His	2660	2665	2670
Ser	Asn	Glu	Glu	Ser	Gly	Phe	Phe	Asn	Glu	Leu	Glu	Ala	Leu	Arg	Ala	2675	2680	2685
Glu	Ser	Val	Ala	Thr	Lys	Ala	Glu	Leu	Ala	Ser	Tyr	Lys	Glu	Lys	Ala	2690	2695	2700
Glu	Lys	Leu	Gln	Glu	Glu	Leu	Leu	Val	Lys	Glu	Thr	Asn	Met	Thr	Ser	2705	2710	2715
Leu	Gln	Lys	Asp	Leu	Ser	Gln	Val	Arg	Asp	His	Leu	Ala	Glu	Ala	Lys	2720		

				2725					2730					2735					
Glu	Lys	Leu	Ser	Ile	Leu	Glu	Lys	Glu	Asp	Glu	Thr	Glu	Val	Gln	Glu				
				2740					2745					2750					
Ser	Lys	Lys	Ala	Cys	Met	Phe	Glu	Pro	Leu	Pro	Ile	Lys	Leu	Ser	Lys				
				2755					2760					2765					
Ser	Ile	Ala	Ser	Gln	Thr	Asp	Gly	Thr	Leu	Lys	Ile	Ser	Ser	Ser	Asn				
				2770					2775					2780					
Gln	Thr	Pro	Gln	Ile	Leu	Val	Lys	Asn	Ala	Gly	Ile	Gln	Ile	Asn	Leu				
2785							2790								2800				
Gln	Ser	Glu	Cys	Ser	Ser	Glu	Glu	Val	Thr	Glu	Ile	Ile	Ser	Gln	Phe				
				2805						2810					2815				
Thr	Glu	Lys	Ile	Glu	Lys	Met	Gln	Glu	Leu	His	Ala	Ala	Glu	Ile	Leu				
				2820						2825					2830				
Asp	Met	Glu	Ser	Arg	His	Ile	Ser	Glu	Thr	Glu	Thr	Leu	Lys	Arg	Glu				
				2835						2840					2845				
His	Tyr	Val	Ala	Val	Gln	Leu	Leu	Lys	Glu	Glu	Cys	Gly	Thr	Leu	Lys				
				2850						2855				2860					
Ala	Val	Ile	Gln	Cys	Leu	Arg	Ser	Lys	Glu	Gly	Ser	Ser	Ile	Pro	Glu				
2865							2870								2880				
Leu	Ala	His	Ser	Asp	Ala	Tyr	Gln	Thr	Arg	Glu	Ile	Cys	Ser	Ser	Asp				
				2885						2890					2895				
Ser	Gly	Ser	Asp	Trp	Gly	Gln	Gly	Ile	Tyr	Leu	Thr	His	Ser	Gln	Gly				
				2900						2905					2910				
Phe	Asp	Ile	Ala	Ser	Glu	Gly	Arg	Gly	Glu	Glu	Ser	Glu	Ser	Ala	Thr				
				2915						2920					2925				
Asp	Ser	Phe	Pro	Lys	Lys	Ile	Lys	Gly	Leu	Leu	Arg	Ala	Val	His	Asn				
				2930											2940				
Glu	Gly	Met	Gln	Val	Leu	Ser	Leu	Thr	Glu	Ser	Pro	Tyr	Ser	Asp	Gly				
2945							2950					2955			2960				
Glu	Asp	His	Ser	Ile	Gln	Gln	Val	Ser	Glu	Pro	Trp	Leu	Glu	Glu	Arg				
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<211> 3925

<212> PRT

<213> Homo sapiens

<400> 6

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Ser Lys Lys Gln Lys Lys Lys Arg Lys Thr Ser Ser Ser Lys His Asp
          35          40          45
Val Ser Ala His His Asp Leu Asn Ile Asp Gln Ser Gln Cys Asn Glu
          50          55          60
Met Tyr Ile Asn Ser Ser Gln Arg Val Glu Ser Thr Val Ile Pro Glu
65          70          75          80
Ser Thr Ile Met Arg Thr Leu His Ser Gly Glu Ile Thr Ser His Glu
          85          90          95
Gln Gly Phe Ser Val Glu Leu Glu Ser Glu Ile Ser Thr Thr Ala Asp
          100          105          110
Asp Cys Ser Ser Glu Val Asn Gly Cys Ser Phe Val Met Arg Thr Gly
          115          120          125
Lys Pro Thr Asn Leu Leu Arg Glu Glu Glu Phe Gly Val Asp Asp Ser
          130          135          140
Tyr Ser Glu Gln Gly Ala Gln Asp Ser Pro Thr His Leu Glu Met Met
145          150          155          160
Glu Ser Glu Leu Ala Gly Lys Gln His Glu Ile Glu Glu Leu Asn Arg
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Glu Leu Glu Glu Met Arg Val Thr Tyr Gly Thr Glu Gly Leu Gln Gln
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225          230          235          240
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Ser Ser Thr Ala Ala Asp Leu Leu Gln Ala Lys Gln Gln Ile Leu Thr
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His Gln Gln Gln Leu Glu Glu Gln Asp His Leu Leu Glu Asp Tyr Gln
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Lys Lys Lys Glu Asp Phe Thr Met Gln Ile Ser Phe Leu Gln Glu Lys
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Ile Lys Val Tyr Glu Met Glu Gln Asp Lys Lys Val Glu Asn Ser Asn
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His	Gln	Gln	Ala	Thr	Glu	Leu	Leu	Arg	Gln	Ala	His	Met	Arg	Gln	Met	1605	1610	1615	
Glu	Arg	Gln	Arg	Glu	Asp	Gln	Glu	Gln	Leu	Gln	Glu	Glu	Ile	Lys	Arg	1620	1625	1630	
Leu	Asn	Arg	Gln	Leu	Ala	Gln	Arg	Ser	Ser	Ile	Asp	Asn	Glu	Asn	Leu	1635	1640	1645	
Val	Ser	Glu	Arg	Glu	Arg	Val	Leu	Leu	Glu	Glu	Leu	Glu	Ala	Leu	Lys	1650	1655	1660	
Gln	Leu	Ser	Leu	Ala	Gly	Arg	Glu	Lys	Leu	Cys	Cys	Glu	Leu	Arg	Asn	1665	1670	1675	1680
Ser	Ser	Thr	Gln	Thr	Gln	Asn	Gly	Asn	Glu	Asn	Gln	Gly	Glu	Val	Glu	1685	1690	1695	
Glu	Gln	Thr	Phe	Lys	Glu	Lys	Glu	Leu	Asp	Arg	Lys	Pro	Glu	Asp	Val	1700	1705	1710	
Pro	Pro	Glu	Ile	Leu	Ser	Asn	Glu	Arg	Tyr	Ala	Leu	Gln	Lys	Ala	Asn	1715	1720	1725	
Asn	Arg	Leu	Leu	Lys	Ile	Leu	Leu	Glu	Val	Val	Lys	Thr	Thr	Ala	Ala				

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Val Glu Glu Thr Ile Gly Arg His Val Leu Gly Ile Leu Asp Arg Ser		
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Ser Lys Ser Gln Ser Ser Ala Ser Leu Ile Trp Arg Ser Glu Ala Glu		1760
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Ala Ser Val Lys Ser Cys Val His Glu Glu His Thr Arg Val Thr Asp		1775
	1780	1785
Glu Ser Ile Pro Ser Tyr Ser Gly Ser Asp Met Pro Arg Asn Asp Ile		1790
	1795	1800
Asn Met Trp Ser Lys Val Thr Glu Glu Gly Thr Glu Leu Ser Gln Arg		1805
	1810	1815
Leu Val Arg Ser Gly Phe Ala Gly Thr Glu Ile Asp Pro Glu Asn Glu		1820
1825	1830	1835
Glu Leu Met Leu Asn Ile Ser Ser Arg Leu Gln Ala Ala Val Glu Lys		1840
	1845	1850
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	1860	1865
Val Thr Gln Thr Glu Leu Met Arg Glu Ser Phe Arg Gln Lys Gln Glu		1870
	1875	1880
Ala Thr Glu Ser Leu Lys Cys Gln Glu Glu Leu Arg Glu Arg Leu His		1885
	1890	1895
Glu Glu Ser Arg Ala Arg Glu Gln Leu Ala Val Glu Leu Ser Lys Ala		1900
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Glu Gly Val Ile Asp Gly Tyr Ala Asp Glu Lys Thr Leu Phe Glu Arg		1920
	1925	1930
Gln Ile Gln Glu Lys Thr Asp Ile Ile Asp Arg Leu Glu Gln Glu Leu		1935
	1940	1945
Leu Cys Ala Ser Asn Arg Leu Gln Glu Leu Glu Ala Glu Gln Gln Gln		1950
	1955	1960
Ile Gln Glu Glu Arg Glu Leu Leu Ser Arg Gln Lys Glu Ala Met Lys		1965
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Ala Glu Ala Gly Pro Val Glu Gln Gln Leu Leu Gln Glu Thr Glu Lys		1980
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	2020	2025
Gln Val Ser Arg Phe Ile Glu Leu Glu Gln Glu Lys Asn Thr Glu Leu		2030
	2035	2040
Met Asp Leu Arg Gln Gln Asn Gln Ala Leu Glu Lys Gln Leu Glu Lys		2045
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2065	2070	2075
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Gly Ala Val Glu Ala Lys Pro Glu Leu Ser Leu Glu Val Gln Leu Gln		2175
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Ala Glu Arg Asp Ala Ile Asp Arg Lys Glu Lys Glu Ile Thr Asn Leu		2190
	2195	2200
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Glu	Val	Gln	Gln	Leu	His	Met	Gln	Leu	Glu	Ile	Gln	Lys	Lys	Glu	Ser	2225	2230	2235
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Leu	Glu	Thr	Arg	Leu	Leu	Gln	Leu	Glu	Ser	Thr	Val	Ser	Ala	Lys	Asp	2500	2505	2510
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Gly	Gln	Phe	Glu	Thr	Glu	Met	Leu	Gln	Lys	Lys	Ile	Val	Asn	Leu	Gln	2530	2535	2540
Lys	Ile	Val	Glu	Glu	Lys	Val	Ala	Ala	Ala	Leu	Val	Ser	Gln	Ile	Gln	2545	2550	2555
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Lys	Thr	Leu	Glu	Asp	Met	Leu	Lys	Ile	His	Thr	Pro	Val	Ser	Gln	Glu
785				790					795						800
Glu	Arg	Leu	Ile	Phe	Leu	Asp	Ser	Ile	Lys	Ser	Lys	Ser	Lys	Asp	Ser
				805					810					815	
Val	Trp	Glu	Lys	Glu	Ile	Glu	Ile	Leu	Ile	Glu	Glu	Asn	Glu	Asp	Leu
		820					825						830		
Lys	Gln	Gln	Cys	Ile	Gln	Leu	Asn	Glu	Glu	Ile	Glu	Lys	Gln	Arg	Asn
	835						840					845			
Thr	Phe	Ser	Phe	Ala	Glu	Lys	Asn	Phe	Glu	Val	Asn	Tyr	Gln	Glu	Leu
	850					855					860				
Gln	Glu	Glu	Tyr	Ala	Cys	Leu	Leu	Lys	Val	Lys	Asp	Asp	Leu	Glu	Asp
865				870					875						880
Ser	Lys	Asn	Lys	Gln	Glu	Leu	Glu	Tyr	Lys	Ser	Lys	Leu	Lys	Ala	Leu
				885					890					895	
Asn	Glu	Glu	Leu	His	Leu	Gln	Arg	Ile	Asn	Pro	Thr	Thr	Val	Lys	Met
			900				905						910		
Lys	Ser	Ser	Val	Phe	Asp	Glu	Asp	Lys	Thr	Phe	Val	Ala	Glu	Thr	Leu
		915					920					925			
Glu	Met	Gly	Glu	Val	Val	Glu	Lys	Asp	Thr	Thr	Glu	Leu	Met	Glu	Lys
	930					935					940				
Leu	Glu	Val	Thr	Lys	Arg	Glu	Lys	Leu	Glu	Leu	Ser	Gln	Arg	Leu	Ser
945				950					955						960
Asp	Leu	Ser	Glu	Gln	Leu	Lys	Gln	Lys	His	Gly	Glu	Ile	Ser	Phe	Leu
				965					970					975	
Asn	Glu	Glu	Val	Lys	Ser	Leu	Lys	Gln	Glu	Lys	Glu	Gln	Val	Ser	Leu
			980					985					990		
Arg	Cys	Arg	Glu	Leu	Glu	Ile	Ile	Ile	Asn	His	Asn	Arg	Ala	Glu	Asn
	995						1000					1005			
Val	Gln	Ser	Cys	Asp	Thr	Gln	Val	Ser	Ser	Leu	Leu	Asp	Gly	Val	Val
	1010					1015					1020				
Thr	Met	Thr	Ser	Arg	Gly	Ala	Glu	Gly	Ser	Val	Ser	Lys	Val	Asn	Lys
1025				1030					1035						1040
Ser	Phe	Gly	Glu	Glu	Ser	Lys	Ile	Met	Val	Glu	Asp	Lys	Val	Ser	Phe
				1045					1050					1055	
Glu	Asn	Met	Thr	Val	Gly	Glu	Glu	Ser	Lys	Gln	Glu	Gln	Leu	Ile	Leu
			1060					1065					1070		
Asp	His	Leu	Pro	Ser	Val	Thr	Lys	Glu	Ser	Ser	Leu	Arg	Ala	Thr	Gln
	1075						1080					1085			
Pro	Ser	Glu	Asn	Asp	Lys	Leu	Gln	Lys	Glu	Leu	Asn	Val	Leu	Lys	Ser
	1090					1095					1100				
Glu	Gln	Asn	Asp	Leu	Arg	Leu	Gln	Met	Glu	Ala	Gln	Arg	Ile	Cys	Leu
1105				1110					1115						1120
Ser	Leu	Val	Tyr	Ser	Thr	His	Val	Asp	Gln	Val	Arg	Glu	Tyr	Met	Glu
				1125					1130					1135	
Asn	Glu	Lys	Asp	Lys	Ala	Leu	Cys	Ser	Leu	Lys	Glu	Glu	Leu	Ile	Phe
			1140					1145					1150		
Ala	Gln	Glu	Glu	Lys	Ile	Lys	Glu	Leu	Gln	Lys	Ile	His	Gln	Leu	Glu
	1155						1160					1165			
Leu	Gln	Thr	Met	Lys	Thr	Gln	Glu	Thr	Gly	Asp	Glu	Gly	Lys	Pro	Leu
	1170					1175					1180				

His	Leu	Leu	Ile	Gly	Lys	Leu	Gln	Lys	Ala	Val	Ser	Glu	Glu	Cys	Ser	1185	1190	1195	1200
Tyr	Phe	Leu	Gln	Thr	Leu	Cys	Ser	Val	Leu	Gly	Glu	Tyr	Tyr	Thr	Pro	1205	1210	1215	
Ala	Leu	Lys	Cys	Glu	Val	Asn	Ala	Glu	Asp	Lys	Glu	Asn	Ser	Gly	Asp	1220	1225	1230	
Tyr	Ile	Ser	Glu	Asn	Glu	Asp	Pro	Glu	Leu	Gln	Asp	Tyr	Arg	Tyr	Glu	1235	1240	1245	
Val	Gln	Asp	Phe	Gln	Glu	Asn	Met	His	Thr	Leu	Leu	Asn	Lys	Val	Thr	1250	1255	1260	
Glu	Glu	Tyr	Asn	Lys	Leu	Leu	Val	Leu	Gln	Thr	Arg	Leu	Ser	Lys	Ile	1265	1270	1275	1280
Trp	Gly	Gln	Gln	Thr	Asp	Gly	Met	Lys	Leu	Glu	Phe	Gly	Glu	Glu	Asn	1285	1290	1295	
Leu	Pro	Lys	Glu	Thr	Glu	Phe	Leu	Ser	Ile	His	Ser	Gln	Met	Thr		1300	1305	1310	
Asn	Leu	Glu	Asp	Ile	Asp	Val	Asn	His	Lys	Ser	Lys	Leu	Ser	Ser	Leu	1315	1320	1325	
Gln	Asp	Leu	Glu	Lys	Thr	Lys	Leu	Glu	Glu	Gln	Val	Gln	Glu	Leu	Glu	1330	1335	1340	
Ser	Leu	Ile	Ser	Ser	Leu	Gln	Gln	Gln	Leu	Lys	Glu	Thr	Glu	Gln	Asn	1345	1350	1355	1360
Tyr	Glu	Ala	Glu	Ile	His	Cys	Leu	Gln	Lys	Arg	Leu	Gln	Ala	Val	Ser	1365	1370	1375	
Glu	Ser	Thr	Val	Pro	Pro	Ser	Leu	Pro	Val	Asp	Ser	Val	Val	Ile	Thr	1380	1385	1390	
Glu	Ser	Asp	Ala	Gln	Arg	Thr	Met	Tyr	Pro	Gly	Ser	Cys	Val	Lys	Lys	1395	1400	1405	
Asn	Ile	Asp	Gly	Thr	Ile	Glu	Phe	Ser	Gly	Glu	Phe	Gly	Val	Lys	Glu	1410	1415	1420	
Glu	Thr	Asn	Ile	Val	Lys	Leu	Leu	Glu	Lys	Gln	Tyr	Gln	Glu	Gln	Leu	1425	1430	1435	1440
Glu	Glu	Glu	Val	Ala	Lys	Val	Ile	Val	Ser	Met	Ser	Ile	Ala	Phe	Ala	1445	1450	1455	
Gln	Gln	Thr	Glu	Leu	Ser	Arg	Ile	Ser	Gly	Gly	Lys	Glu	Asn	Thr	Ala	1460	1465	1470	
Ser	Ser	Lys	Gln	Ala	His	Ala	Val	Cys	Gln	Gln	Glu	Gln	His	Tyr	Phe	1475	1480	1485	
Asn	Glu	Met	Lys	Leu	Ser	Gln	Asp	Gln	Ile	Gly	Phe	Gln	Thr	Phe	Glu	1490	1495	1500	
Thr	Val	Asp	Val	Lys	Phe	Lys	Glu	Glu	Phe	Lys	Pro	Leu	Ser	Lys	Glu	1505	1510	1515	1520
Leu	Gly	Glu	His	Gly	Lys	Glu	Ile	Leu	Leu	Ser	Asn	Ser	Asp	Pro	His	1525	1530	1535	
Asp	Ile	Pro	Glu	Ser	Lys	Asp	Cys	Val	Leu	Thr	Ile	Ser	Glu	Glu	Met	1540	1545	1550	
Phe	Ser	Lys	Asp	Lys	Thr	Phe	Ile	Val	Arg	Gln	Ser	Ile	His	Asp	Glu	1555	1560	1565	
Ile	Ser	Val	Ser	Ser	Met	Asp	Ala	Ser	Arg	Gln	Leu	Met	Leu	Asn	Glu	1570	1575	1580	
Glu	Gln	Leu	Glu	Asp	Met	Arg	Gln	Glu	Leu	Val	Arg	Gln	Tyr	Gln	Glu	1585	1590	1595	1600
His	Gln	Gln	Ala	Thr	Glu	Leu	Leu	Arg	Gln	Ala	His	Met	Arg	Gln	Met	1605	1610	1615	
Glu	Arg	Gln	Arg	Glu	Asp	Gln	Glu	Gln	Leu	Gln	Glu	Glu	Ile	Lys	Arg	1620	1625	1630	
Leu	Asn	Arg	Gln	Leu	Ala	Gln	Arg	Ser	Ser	Ile	Asp	Asn	Glu	Asn	Leu	1635	1640	1645	
Val	Ser	Glu	Arg	Glu	Arg	Val	Leu	Leu	Glu	Glu	Leu	Glu	Ala	Leu	Lys				

1650	1655	1660
Gln Leu Ser Leu Ala Gly Arg Glu Lys Leu Cys Cys Glu Leu Arg Asn		
1665	1670	1675
Ser Ser Thr Gln Thr Gln Asn Gly Asn Glu Asn Gln Gly Glu Val Glu		1680
	1685	1690
Glu Gln Thr Phe Lys Glu Lys Glu Leu Asp Arg Lys Pro Glu Asp Val		1695
	1700	1705
Pro Pro Glu Ile Leu Ser Asn Glu Arg Tyr Ala Leu Gln Lys Ala Asn		1710
	1715	1720
Asn Arg Leu Leu Lys Ile Leu Leu Glu Val Val Lys Thr Thr Ala Ala		1725
	1730	1735
Val Glu Glu Thr Ile Gly Arg His Val Leu Gly Ile Leu Asp Arg Ser		1740
1745	1750	1755
Ser Lys Ser Gln Ser Ser Ala Ser Leu Ile Trp Arg Ser Glu Ala Glu		1760
	1765	1770
Ala Ser Val Lys Ser Cys Val His Glu Glu His Thr Arg Val Thr Asp		1775
	1780	1785
Glu Ser Ile Pro Ser Tyr Ser Gly Ser Asp Met Pro Arg Asn Asp Ile		1790
	1795	1800
Asn Met Trp Ser Lys Val Thr Glu Glu Gly Thr Glu Leu Ser Gln Arg		1805
	1810	1815
Leu Val Arg Ser Gly Phe Ala Gly Thr Glu Ile Asp Pro Glu Asn Glu		1820
1825	1830	1835
Glu Leu Met Leu Asn Ile Ser Ser Arg Leu Gln Ala Ala Val Glu Lys		1840
	1845	1850
Leu Leu Glu Ala Ile Ser Glu Thr Ser Ser Gln Leu Glu His Ala Lys		1855
	1860	1865
Val Thr Gln Thr Glu Leu Met Arg Glu Ser Phe Arg Gln Lys Gln Glu		1870
	1875	1880
Ala Thr Glu Ser Leu Lys Cys Gln Glu Glu Leu Arg Glu Arg Leu His		1885
	1890	1895
Glu Glu Ser Arg Ala Arg Glu Gln Leu Ala Val Glu Leu Ser Lys Ala		1900
1905	1910	1915
Glu Gly Val Ile Asp Gly Tyr Ala Asp Glu Lys Thr Leu Phe Glu Arg		1920
	1925	1930
Gln Ile Gln Glu Lys Thr Asp Ile Ile Asp Arg Leu Glu Gln Glu Leu		1935
	1940	1945
Leu Cys Ala Ser Asn Arg Leu Gln Glu Leu Glu Ala Glu Gln Gln Gln		1950
	1955	1960
Ile Gln Glu Glu Arg Glu Leu Leu Ser Arg Gln Lys Glu Ala Met Lys		1965
	1970	1975
Ala Glu Ala Gly Pro Val Glu Gln Gln Leu Leu Gln Glu Thr Glu Lys		1980
1985	1990	1995
Leu Met Lys Glu Lys Leu Glu Val Gln Cys Gln Ala Glu Lys Val Arg		2000
	2005	2010
Asp Asp Leu Gln Lys Gln Val Lys Ala Leu Glu Ile Asp Val Glu Glu		2015
	2020	2025
Gln Val Ser Arg Phe Ile Glu Leu Glu Gln Glu Lys Asn Thr Glu Leu		2030
	2035	2040
Met Asp Leu Arg Gln Gln Asn Gln Ala Leu Glu Lys Gln Leu Glu Lys		2045
	2050	2055
Met Arg Lys Phe Leu Asp Glu Gln Ala Ile Asp Arg Glu His Glu Arg		2060
2065	2070	2075
Asp Val Phe Gln Gln Glu Ile Gln Lys Leu Glu Gln Gln Leu Lys Val		2080
	2085	2090
Val Pro Arg Phe Gln Pro Ile Ser Glu His Gln Thr Arg Glu Val Glu		2095
	2100	2105
Gln Leu Ala Asn His Leu Lys Glu Lys Thr Asp Lys Cys Ser Glu Leu		2110
	2115	2120
		2125

Leu	Leu	Ser	Lys	Glu	Gln	Leu	Gln	Arg	Asp	Ile	Gln	Glu	Arg	Asn	Glu
2130						2135					2140				
Glu	Ile	Glu	Lys	Leu	Glu	Phe	Arg	Val	Arg	Glu	Leu	Glu	Gln	Ala	Leu
2145					2150					2155					2160
Leu	Val	Glu	Asp	Arg	Lys	His	Phe	Gly	Ala	Val	Glu	Ala	Lys	Pro	Glu
			2165						2170					2175	
Leu	Ser	Leu	Glu	Val	Gln	Leu	Gln	Ala	Glu	Arg	Asp	Ala	Ile	Asp	Arg
			2180					2185						2190	
Lys	Glu	Lys	Glu	Ile	Thr	Asn	Leu	Glu	Glu	Gln	Leu	Glu	Gln	Phe	Arg
		2195					2200					2205			
Glu	Glu	Leu	Glu	Asn	Lys	Asn	Glu	Glu	Val	Gln	Gln	Leu	His	Met	Gln
2210						2215					2220				
Leu	Glu	Ile	Gln	Lys	Lys	Glu	Ser	Thr	Thr	Arg	Leu	Gln	Glu	Leu	Glu
2225					2230					2235					2240
Gln	Glu	Asn	Lys	Leu	Phe	Lys	Asp	Asp	Met	Glu	Lys	Leu	Gly	Leu	Ala
			2245						2250					2255	
Ile	Lys	Glu	Ser	Asp	Ala	Met	Ser	Thr	Gln	Asp	Gln	His	Val	Leu	Phe
			2260						2265					2270	
Gly	Lys	Phe	Ala	Gln	Ile	Ile	Gln	Glu	Lys	Glu	Val	Glu	Ile	Asp	Gln
		2275					2280						2285		
Leu	Asn	Glu	Gln	Val	Thr	Lys	Leu	Gln	Gln	Gln	Leu	Lys	Ile	Thr	Thr
2290						2295					2300				
Asp	Asn	Lys	Val	Ile	Glu	Glu	Lys	Asn	Glu	Leu	Ile	Arg	Asp	Leu	Glu
2305					2310					2315					2320
Thr	Gln	Ile	Glu	Cys	Leu	Met	Ser	Asp	Gln	Glu	Cys	Val	Lys	Arg	Asn
			2325						2330					2335	
Arg	Glu	Glu	Glu	Ile	Glu	Gln	Leu	Asn	Glu	Val	Ile	Glu	Lys	Leu	Gln
			2340					2345						2350	
Gln	Glu	Leu	Ala	Asn	Ile	Gly	Gln	Lys	Thr	Ser	Met	Asn	Ala	His	Ser
		2355				2360						2365			
Leu	Ser	Glu	Glu	Ala	Asp	Ser	Leu	Lys	His	Gln	Leu	Asp	Val	Val	Ile
2370						2375					2380				
Ala	Glu	Lys	Leu	Ala	Leu	Glu	Gln	Gln	Val	Glu	Thr	Ala	Asn	Glu	Glu
2385					2390					2395					2400
Met	Thr	Phe	Met	Lys	Asn	Val	Leu	Lys	Glu	Thr	Asn	Phe	Lys	Met	Asn
			2405						2410					2415	
Gln	Leu	Thr	Gln	Glu	Leu	Phe	Ser	Leu	Lys	Arg	Glu	Arg	Glu	Ser	Val
			2420					2425						2430	
Glu	Lys	Ile	Gln	Ser	Ile	Pro	Glu	Asn	Ser	Val	Asn	Val	Ala	Ile	Asp
		2435					2440					2445			
His	Leu	Ser	Lys	Asp	Lys	Pro	Glu	Leu	Glu	Val	Val	Leu	Thr	Glu	Asp
2450					2455						2460				
Ala	Leu	Lys	Ser	Leu	Glu	Asn	Gln	Thr	Tyr	Phe	Lys	Ser	Phe	Glu	Glu
2465					2470					2475					2480
Asn	Gly	Lys	Gly	Ser	Ile	Ile	Asn	Leu	Glu	Thr	Arg	Leu	Leu	Gln	Leu
			2485					2490						2495	
Glu	Ser	Thr	Val	Ser	Ala	Lys	Asp	Leu	Glu	Leu	Thr	Gln	Cys	Tyr	Lys
			2500					2505					2510		
Gln	Ile	Lys	Asp	Met	Gln	Glu	Gln	Gly	Gln	Phe	Glu	Thr	Glu	Met	Leu
		2515					2520					2525			
Gln	Lys	Lys	Ile	Val	Asn	Leu	Gln	Lys	Ile	Val	Glu	Glu	Lys	Val	Ala
2530						2535						2540			
Ala	Ala	Leu	Val	Ser	Gln	Ile	Gln	Leu	Glu	Ala	Val	Gln	Glu	Tyr	Ala
2545					2550					2555					2560
Lys	Phe	Cys	Gln	Asp	Asn	Gln	Thr	Ile	Ser	Ser	Glu	Pro	Glu	Arg	Thr
			2565					2570						2575	
Asn	Ile	Gln	Asn	Leu	Asn	Gln	Leu	Arg	Glu	Asp	Glu	Leu	Gly	Ser	Asp
		2580						2585					2590		
Ile	Ser	Ala	Leu	Thr	Leu	Arg	Ile	Ser	Glu	Leu	Glu	Ser	Gln	Val	Val

2595	2600	2605
Glu Met His Thr Ser Leu Ile Leu Glu Lys Glu Gln Val Glu Ile Ala		
2610	2615	2620
Glu Lys Asn Val Leu Glu Lys Glu Lys Lys Leu Leu Glu Leu Gln Lys		
2625	2630	2635
Leu Leu Glu Gly Asn Glu Lys Lys Gln Arg Glu Lys Glu Lys Lys Arg		2640
2645	2650	2655
Ser Pro Gln Asp Val Glu Val Leu Lys Thr Thr Thr Glu Leu Phe His		
2660	2665	2670
Ser Asn Glu Glu Ser Gly Phe Phe Asn Glu Leu Glu Ala Leu Arg Ala		
2675	2680	2685
Glu Ser Val Ala Thr Lys Ala Glu Leu Ala Ser Tyr Lys Glu Lys Ala		
2690	2695	2700
Glu Lys Leu Gln Glu Glu Leu Leu Val Lys Glu Thr Asn Met Thr Ser		
2705	2710	2715
Leu Gln Lys Asp Leu Ser Gln Val Arg Asp His Leu Ala Glu Ala Lys		2720
2725	2730	2735
Glu Lys Leu Ser Ile Leu Glu Lys Glu Asp Glu Thr Glu Val Gln Glu		
2740	2745	2750
Ser Lys Lys Ala Cys Met Phe Glu Pro Leu Pro Ile Lys Leu Ser Lys		
2755	2760	2765
Ser Ile Ala Ser Gln Thr Asp Gly Thr Leu Lys Ile Ser Ser Ser Asn		
2770	2775	2780
Gln Thr Pro Gln Ile Leu Val Lys Asn Ala Gly Ile Gln Ile Asn Leu		
2785	2790	2795
Gln Ser Glu Cys Ser Ser Glu Glu Val Thr Glu Ile Ile Ser Gln Phe		2800
2805	2810	2815
Thr Glu Lys Ile Glu Lys Met Gln Glu Leu His Ala Ala Glu Ile Leu		
2820	2825	2830
Asp Met Glu Ser Arg His Ile Ser Glu Thr Glu Thr Leu Lys Arg Glu		
2835	2840	2845
His Tyr Val Ala Val Gln Leu Leu Lys Glu Glu Cys Gly Thr Leu Lys		
2850	2855	2860
Ala Val Ile Gln Cys Leu Arg Ser Lys Glu Gly Ser Ser Ile Pro Glu		
2865	2870	2875
Leu Ala His Ser Asp Ala Tyr Gln Thr Arg Glu Ile Cys Ser Ser Asp		2880
2885	2890	2895
Ser Gly Ser Asp Trp Gly Gln Gly Ile Tyr Leu Thr His Ser Gln Gly		
2900	2905	2910
Phe Asp Ile Ala Ser Glu Gly Arg Gly Glu Glu Ser Glu Ser Ala Thr		
2915	2920	2925
Asp Ser Phe Pro Lys Lys Ile Lys Gly Leu Leu Arg Ala Val His Asn		
2930	2935	2940
Glu Gly Met Gln Val Leu Ser Leu Thr Glu Ser Pro Tyr Ser Asp Gly		
2945	2950	2955
Glu Asp His Ser Ile Gln Gln Val Ser Glu Pro Trp Leu Glu Glu Arg		2960
2965	2970	2975
Lys Ala Tyr Ile Asn Thr Ile Ser Ser Leu Lys Asp Leu Ile Thr Lys		
2980	2985	2990
Met Gln Leu Gln Arg Glu Ala Glu Val Tyr Asp Ser Ser Gln Ser His		
2995	3000	3005
Glu Ser Phe Ser Asp Trp Arg Gly Glu Leu Leu Leu Ala Leu Gln Gln		
3010	3015	3020
Val Phe Leu Glu Glu Arg Ser Val Leu Leu Ala Ala Phe Arg Thr Glu		
3025	3030	3035
Leu Thr Ala Leu Gly Thr Thr Asp Ala Val Gly Leu Leu Asn Cys Leu		3040
3045	3050	3055
Glu Gln Arg Ile Gln Glu Gln Gly Val Glu Tyr Gln Ala Ala Met Glu		
3060	3065	3070

Cys	Leu	Gln	Lys	Ala	Asp	Arg	Arg	Ser	Leu	Leu	Ser	Glu	Ile	Gln	Ala	3075	3080	3085
Leu	His	Ala	Gln	Met	Asn	Gly	Arg	Lys	Ile	Thr	Leu	Lys	Arg	Glu	Gln	3090	3095	3100
Glu	Ser	Glu	Lys	Pro	Ser	Gln	Glu	Leu	Leu	Glu	Tyr	Asn	Ile	Gln	Gln	3105	3110	3115
Lys	Gln	Ser	Gln	Met	Leu	Glu	Met	Gln	Val	Glu	Leu	Ser	Ser	Met	Lys	3125	3130	3135
Asp	Arg	Ala	Thr	Glu	Leu	Gln	Glu	Gln	Leu	Ser	Ser	Glu	Lys	Met	Val	3140	3145	3150
Val	Ala	Glu	Leu	Lys	Ser	Glu	Leu	Ala	Gln	Thr	Lys	Leu	Glu	Leu	Glu	3155	3160	3165
Thr	Thr	Leu	Lys	Ala	Gln	His	Lys	His	Leu	Lys	Glu	Leu	Glu	Ala	Phe	3170	3175	3180
Arg	Leu	Glu	Val	Lys	Asp	Lys	Thr	Asp	Glu	Val	His	Leu	Leu	Asn	Asp	3185	3190	3195
Thr	Leu	Ala	Ser	Glu	Gln	Lys	Lys	Ser	Arg	Glu	Leu	Gln	Trp	Ala	Leu	3205	3210	3215
Glu	Lys	Glu	Lys	Ala	Lys	Leu	Gly	Arg	Ser	Glu	Glu	Arg	Asp	Lys	Glu	3220	3225	3230
Glu	Leu	Glu	Asp	Leu	Lys	Phe	Ser	Leu	Glu	Ser	Gln	Lys	Gln	Arg	Asn	3235	3240	3245
Leu	Gln	Leu	Asn	Leu	Leu	Leu	Glu	Gln	Gln	Lys	Gln	Leu	Leu	Asn	Glu	3250	3255	3260
Ser	Gln	Gln	Lys	Ile	Glu	Ser	Gln	Arg	Met	Leu	Tyr	Asp	Ala	Gln	Leu	3265	3270	3275
Ser	Glu	Glu	Gln	Gly	Arg	Asn	Leu	Glu	Leu	Gln	Val	Leu	Leu	Glu	Ser	3285	3290	3295
Glu	Lys	Val	Arg	Ile	Arg	Glu	Met	Ser	Ser	Thr	Leu	Asp	Arg	Glu	Arg	3300	3305	3310
Glu	Leu	His	Ala	Gln	Leu	Gln	Ser	Ser	Asp	Gly	Thr	Gly	Gln	Ser	Arg	3315	3320	3325
Pro	Pro	Leu	Pro	Ser	Glu	Asp	Leu	Leu	Lys	Glu	Leu	Gln	Lys	Gln	Leu	3330	3335	3340
Glu	Glu	Lys	His	Ser	Arg	Ile	Val	Glu	Leu	Leu	Asn	Glu	Thr	Glu	Lys	3345	3350	3355
Tyr	Lys	Leu	Asp	Ser	Leu	Gln	Thr	Arg	Gln	Gln	Met	Glu	Lys	Asp	Arg	3365	3370	3375
Gln	Val	His	Arg	Lys	Thr	Leu	Gln	Thr	Glu	Gln	Glu	Ala	Asn	Thr	Glu	3380	3385	3390
Gly	Gln	Lys	Lys	Met	His	Glu	Leu	Gln	Ser	Lys	Val	Glu	Asp	Leu	Gln	3395	3400	3405
Arg	Gln	Leu	Glu	Glu	Lys	Arg	Gln	Gln	Val	Tyr	Lys	Leu	Asp	Leu	Glu	3410	3415	3420
Gly	Gln	Arg	Leu	Gln	Gly	Ile	Met	Gln	Glu	Phe	Gln	Lys	Gln	Glu	Leu	3425	3430	3435
Glu	Arg	Glu	Glu	Lys	Arg	Glu	Ser	Arg	Arg	Ile	Leu	Tyr	Gln	Asn	Leu	3445	3450	3455
Asn	Glu	Pro	Thr	Thr	Trp	Ser	Leu	Thr	Ser	Asp	Arg	Thr	Arg	Asn	Trp	3460	3465	3470
Val	Leu	Gln	Gln	Lys	Ile	Glu	Gly	Glu	Thr	Lys	Glu	Ser	Asn	Tyr	Ala	3475	3480	3485
Lys	Leu	Ile	Glu	Met	Asn	Gly	Gly	Gly	Thr	Gly	Cys	Asn	His	Glu	Leu	3490	3495	3500
Glu	Met	Ile	Arg	Gln	Lys	Leu	Gln	Cys	Val	Ala	Ser	Lys	Leu	Gln	Val	3505	3510	3515
Leu	Pro	Gln	Lys	Ala	Ser	Glu	Arg	Leu	Gln	Phe	Glu	Thr	Ala	Asp	Asp	3525	3530	3535
Glu	Asp	Phe	Ile	Trp	Val	Gln	Glu	Asn	Ile	Asp	Glu	Ile	Ile	Leu	Gln			

3540	3545	3550
Leu Gln Lys Leu Thr Gly Gln Gln Gly Glu Glu Pro Ser Leu Val Ser		
3555	3560	3565
Pro Ser Thr Ser Cys Gly Ser Leu Thr Glu Arg Leu Leu Arg Gln Asn		
3570	3575	3580
Ala Glu Leu Thr Gly His Ile Ser Gln Leu Thr Glu Glu Lys Asn Asp		
3585	3590	3595
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<211> 2850

<212> DNA

<213> Homo sapiens

<400> 9

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 <213> Homo sapiens

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 Ser Ser Ile Phe Ile Glu Asp Ala Ile Lys Tyr Phe Lys Glu Lys Val
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<211> 414
<212> PRT
<213> Homo sapiens

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Arg Val Gln Gln Asn Val Pro Ser Gly Thr Asp Thr Gly Asp Pro Gln
50 55 60
Ser Lys Pro Leu Gly Asp Trp Ala Ala Gly Thr Met Asp Pro Glu Ser
65 70 75 80
Ser Ile Phe Ile Glu Asp Ala Ile Lys Tyr Phe Lys Glu Lys Val Ser
85 90 95

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Phe	Val	Ala	Ala	Ala	Glu	Leu	Pro	Arg	Asn	Glu	Ala	Asp	Glu	Leu	Arg
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Lys	Ala	Leu	Asp	Asn	Leu	Ala	Arg	Gln	Met	Ile	Met	Lys	Asp	Lys	Asn
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Ser	Ser	Thr	Ile	Asp	Tyr	Gly	Lys	Lys	Trp	Trp	Thr	Gln	Ala	Gln	Ala
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<210> 14
<211> 331
<212> PRT
<213> Homo sapiens

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Glu Lys Leu Arg Ala Leu Ala Asn Gly Ile Glu Glu Val His Arg Gly
100 105 110
Cys Thr Ile Ser Asn Val Val Ser Ser Thr Gly Ala Ala Ser Gly
115 120 125
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Ser Leu Ala Leu Thr Ala Ala Gly Val Gly Leu Gly Ala Ala Ser Ala
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Val Thr Gly Ile Thr Thr Ser Ile Val Glu His Ser Tyr Thr Ser Ser
165 170 175
Ala Glu Ala Glu Ala Ser Arg Leu Thr Ala Thr Ser Ile Asp Arg Leu
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Arg	Arg	Gln	Ala	Gln	Glu	Leu	Glu	Glu	Asn	Leu	Met	Glu	Leu	Thr	Gln
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 <212> DNA
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 <211> 265
 <212> PRT
 <213> Homo sapiens

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Gln	Ile	Ser	Leu	Leu	Arg	Ala	Phe	Phe	Tyr	Val	Ala	Ala	Gln	Leu	Val
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Cys	Ile	Phe	Ala	Ser	Thr	Asp	Ser	Arg	Arg	Thr	Ser	Pro	Val	Gly	Ser
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Pro	Ala	Leu	Ser	Ile	Gly	Leu	Ser	Val	Thr	Leu	Gly	His	Leu	Val	Gly
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Ile	Tyr	Phe	Thr	Gly	Cys	Ser	Met	Asn	Pro	Ala	Arg	Ser	Phe	Gly	Pro
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Ala	Val	Val	Met	Asn	Arg	Phe	Ser	Pro	Ala	His	Trp	Val	Phe	Trp	Val
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	210					215					220				
Leu	Phe	Pro	Asn	Ser	Leu	Ser	Leu	Ser	Glu	Arg	Val	Ala	Ile	Ile	Lys
225				230					235						240
Gly	Thr	Tyr	Glu	Pro	Asp	Glu	Asp	Trp	Glu	Glu	Gln	Arg	Glu	Glu	Arg
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 <213> Homo sapiens

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 <213> Homo sapiens

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 <213> Homo sapiens

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 <211> 180
 <212> PRT
 <213> Homo sapiens

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 Asn Ser Glu Ala Cys Arg Asp Gly Leu Arg Ala Val Met Glu Cys Arg
 50 55 60
 Asn Val Thr His Leu Leu Gln Gln Glu Leu Thr Glu Ala Gln Lys Gly
 65 70 75 80
 Phe Gln Asp Val Glu Ala Gln Ala Ala Thr Cys Asn His Thr Val Met
 85 90 95
 Ala Leu Met Ala Ser Leu Asp Ala Glu Lys Ala Gln Gly Gln Lys Lys
 100 105 110
 Val Glu Glu Leu Glu Gly Glu Ile Thr Thr Leu Asn His Lys Leu Gln
 115 120 125

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Ser	Val	Arg	Ile	Ala	Asp	Lys	Lys	Tyr	Tyr	Pro	Ser	Ser	Gln	Asp	Ser
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Ser	Ser	Ala	Ala	Ala	Pro	Gln	Leu	Leu	Ile	Val	Leu	Leu	Gly	Leu	Ser
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<400> 21

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 <211> 244
 <212> PRT
 <213> Homo sapiens

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 Asp Pro Gly Asp Thr Trp Lys Asp Tyr Cys Thr Leu Val Thr Ile Ala
 50 55 60
 Lys Ser Leu Leu Asp Leu Asn Lys Tyr Arg Pro Ile Gln Thr Pro Ser
 65 70 75 80
 Val Cys Ser Asp Ser Leu Glu Ser Pro Asp Glu Asp Met Gly Ser Asp
 85 90 95
 Ser Asp Val Thr Thr Glu Ser Gly Ser Ser Pro Ser His Ser Pro Glu
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<210> 23
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 <212> DNA
 <213> Homo sapiens

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 <212> PRT
 <213> Homo sapiens

<400> 24

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 Asp Trp Lys Val Phe Glu Ser Trp Met His His Trp Leu Leu Phe Glu
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 Met Ser Arg His Ser Leu Glu Gln Lys Pro Thr Asp Ala Pro Pro Lys
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 <212> PRT
 <213> Homo sapiens

<400> 26
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 Ser Lys Val Gln Thr Thr Pro Ser Lys Pro Gly Gly Asp Arg Tyr Ile
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 Pro His Arg Ser Ala Ala Gln Met Glu Val Ala Ser Phe Leu Leu Ser
 85 90 95
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 115 120 125
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 130 135 140
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 Ser Arg Lys Thr Cys Arg Tyr Ile Pro Ser Leu Pro Asp Arg Ile Leu
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 Asp Ala Pro Glu Ile Arg Asn Asp Tyr Tyr Leu Asn Leu Val Asp Trp
 180 185 190
 Ser Ser Gly Asn Val Leu Ala Val Ala Leu Asp Asn Ser Val Tyr Leu
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 Pro Gly Glu Tyr Ile Ser Ser Val Ala Trp Ile Lys Glu Gly Asn Tyr
 225 230 235 240
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 Gln Gln Lys Arg Leu Arg Asn Met Thr Ser His Ser Ala Arg Val Gly
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<210> 28
 <211> 168
 <212> PRT
 <213> Homo sapiens

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 35 40 45
 Asn Pro Glu Ile Ala Arg Arg Leu Leu Leu Arg Gly Ala Asn Pro Asp
 50 55 60
 Leu Lys Asp Arg Thr Gly Phe Ala Val Ile His Asp Ala Ala Arg Ala
 65 70 75 80
 Gly Phe Leu Asp Thr Leu Gln Thr Leu Leu Glu Phe Gln Ala Asp Val
 85 90 95
 Asn Ile Glu Asp Asn Glu Gly Asn Leu Pro Leu His Leu Ala Ala Lys
 100 105 110
 Glu Gly His Leu Arg Val Val Glu Phe Leu Val Lys His Thr Ala Ser
 115 120 125
 Asn Val Gly His Arg Asn His Lys Gly Asp Thr Ala Cys Asp Leu Ala
 130 135 140
 Arg Leu Tyr Gly Arg Asn Glu Val Val Ser Leu Met Gln Ala Asn Gly
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<211> 184
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<213> Homo sapiens

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Ile Pro Pro Pro Asp Lys Ala Gln His Asn Asp Ser Glu Gln Thr Gln
35 40 45
Ser Pro Gln Gln Pro Gly Ser Arg Asn Arg Gly Arg Gly Gln Gly Arg

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Leu His Val Thr	Glu Arg Lys Tyr Leu Lys Arg	Asp Trp Cys Lys Thr		
	85	90	95	
Gln Pro Leu Lys	Gln Thr Ile His Glu Glu Gly	Cys Asn Ser Arg Thr		
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Ile Ile Asn Arg Phe	Cys Tyr Gly Gln Cys Asn	Ser Phe Tyr Ile Pro		
	115	120	125	
Arg His Ile Arg Lys	Glu Glu Gly Ser Phe Gln	Ser Cys Ser Phe Cys		
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 <212> DNA
 <213> Homo sapiens

<400> 31

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 <213> Homo sapiens

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<211> 5064

<212> DNA

<213> Homo sapiens

<400> 41

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<210> 42

<211> 1224

<212> PRT

<213> Homo sapiens

<400> 42

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Ile Gln Leu Trp Asp Tyr Arg Met Cys Thr Leu Ile Asp Lys Phe Asp
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Glu His Asp Gly Pro Val Arg Gly Ile Asp Phe His Lys Gln Gln Pro
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Leu Phe Val Ser Gly Gly Asp Asp Tyr Lys Ile Lys Val Trp Asn Tyr
65          70          75          80
Lys Leu Arg Arg Cys Leu Phe Thr Leu Leu Gly His Leu Asp Tyr Ile
          85          90          95
Arg Thr Thr Phe Phe His His Glu Tyr Pro Trp Ile Leu Ser Ala Ser
          100          105          110
Asp Asp Gln Thr Ile Arg Val Trp Asn Trp Gln Ser Arg Thr Cys Val
          115          120          125
Cys Val Leu Thr Gly His Asn His Tyr Val Met Cys Ala Gln Phe His
          130          135          140
Pro Thr Glu Asp Leu Val Val Ser Ala Ser Leu Asp Gln Thr Val Arg
145          150          155          160
Val Trp Asp Ile Ser Gly Leu Arg Lys Lys Asn Leu Ser Pro Gly Ala
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Val Glu Ser Asp Val Arg Gly Ile Thr Gly Val Asp Leu Phe Gly Thr
          180          185          190
Thr Asp Ala Val Val Lys His Val Leu Glu Gly His Asp Arg Gly Val
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Asn Trp Ala Ala Phe His Pro Thr Met Pro Leu Ile Val Ser Gly Ala
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Asp Asp Arg Gln Val Lys Ile Trp Arg Met Asn Glu Ser Lys Ala Trp
225          230          235          240
Glu Val Asp Thr Cys Arg Gly His Tyr Asn Asn Val Ser Cys Ala Val
          245          250          255
Phe His Pro Arg Gln Glu Leu Ile Leu Ser Asn Ser Glu Asp Lys Ser
          260          265          270
Ile Arg Val Trp Asp Met Ser Lys Arg Thr Gly Val Gln Thr Phe Arg
          275          280          285
Arg Asp His Asp Arg Phe Trp Val Leu Ala Ala His Pro Asn Leu Asn
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Leu Phe Ala Ala Gly His Asp Gly Gly Met Ile Val Phe Lys Leu Glu
305          310          315          320
Arg Glu Arg Pro Ala Tyr Ala Val His Gly Asn Met Leu His Tyr Val
          325          330          335
Lys Asp Arg Phe Leu Arg Gln Leu Asp Phe Asn Ser Ser Lys Asp Val
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Ser Tyr Asn Pro Ala Glu Asn Ala Val Leu Leu Cys Thr Arg Ala Ser
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Thr	Ala	Val	Trp	Val	Ala	Arg	Asn	Arg	Phe	Ala	Val	Leu	Asp	Arg	Met
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His	Ser	Leu	Leu	Ile	Lys	Asn	Leu	Lys	Asn	Glu	Ile	Thr	Lys	Lys	Val
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Gln	Val	Pro	Asn	Cys	Asp	Glu	Ile	Phe	Tyr	Ala	Gly	Thr	Gly	Asn	Leu
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Arg	Thr	Leu	Ala	Ser	Val	Lys	Ile	Ser	Lys	Val	Lys	Tyr	Val	Ile	Trp
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Ser	Ala	Asp	Met	Ser	His	Val	Ala	Leu	Leu	Ala	Lys	His	Ala	Ile	Val
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Ile	Arg	Thr	Leu	Asp	Leu	Pro	Ile	Tyr	Val	Thr	Arg	Val	Lys	Gly	Asn
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Asn	Val	Tyr	Cys	Leu	Asp	Arg	Glu	Cys	Arg	Pro	Arg	Val	Leu	Thr	Ile
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Asp	Pro	Thr	Glu	Phe	Lys	Phe	Lys	Leu	Ala	Leu	Ile	Asn	Arg	Lys	Tyr
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Phe	Val	Lys	Asp	Glu	Lys	Thr	Arg	Phe	Ser	Leu	Ala	Leu	Glu	Cys	Gly
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	885	890
Gly Ala Ala Gly Gly Ala Glu Asp Gly Phe Phe Val Pro Pro Thr Lys		895
	900	905
Gly Thr Ser Pro Thr Gln Ile Trp Cys Asn Asn Ser Gln Leu Pro Val		910
	915	920
Asp His Ile Leu Ala Gly Ser Phe Glu Thr Ala Met Arg Leu Leu His		925
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Asp Gln Val Gly Val Ile Gln Phe Gly Pro Tyr Lys Gln Leu Phe Leu		940
	945	950
Gln Thr Tyr Ala Arg Gly Arg Thr Thr Tyr Gln Ala Leu Pro Cys Leu		955
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Pro Ser Met Tyr Gly Tyr Pro Asn Arg Asn Trp Lys Asp Ala Gly Leu		975
	980	985
Lys Asn Gly Val Pro Ala Val Gly Leu Lys Leu Asn Asp Leu Ile Gln		990
	995	1000
Arg Leu Gln Leu Cys Tyr Gln Leu Thr Thr Val Gly Lys Phe Glu Glu		1005
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Ala Val Glu Lys Phe Arg Ser Ile Leu Leu Ser Val Pro Leu Leu Val		1020
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Val Asp Asn Lys Gln Glu Ile Ala Glu Ala Gln Gln Leu Ile Thr Ile		1035
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Cys Arg Glu Tyr Ile Val Gly Leu Ser Val Glu Thr Glu Arg Lys Lys		1055
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Ala Tyr Phe Thr His Ser Asn Leu Gln Pro Val His Met Ile Leu Val		1085
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Leu Arg Thr Ala Leu Asn Leu Phe Phe Lys Leu Lys Asn Phe Lys Thr		1100
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Cys Ala Ala Ser Tyr Arg Pro Ile Tyr Arg Gly Lys Pro Val Glu Lys		1165
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Cys Pro Leu Ser Gly Ala Cys Tyr Ser Pro Glu Phe Lys Gly Gln Ile		1180
	1185	1190
Cys Arg Val Thr Thr Val Thr Glu Ile Gly Lys Asp Val Ile Gly Leu		1195
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<210> 43

<211> 266

<212> DNA

<213> Homo sapiens

<400> 43

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<210> 44

<211> 77

<212> PRT

<213> Homo sapiens

<400> 44

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			20					25					30		
Lys	Cys	Gly	Lys	Thr	Leu	Thr	Ser	Gly	Gly	His	Ala	Glu	His	Glu	Gly
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Lys	Pro	Tyr	Cys	Asn	His	Pro	Cys	Tyr	Ala	Ala	Met	Phe	Gly	Pro	Lys
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<210> 45

<211> 2312

<212> DNA

<213> Homo sapiens

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<210> 46

<211> 349

<212> PRT

<213> Homo sapiens

<400> 46

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20      25      30
Cys Arg Cys Pro Asp Glu Pro Ala Pro Arg Cys Pro Ala Gly Val Ser
35      40      45
Leu Val Leu Asp Gly Cys Gly Cys Cys Arg Val Cys Ala Lys Gln Leu
50      55      60
Gly Glu Leu Cys Thr Glu Arg Asp Pro Cys Asp Pro His Lys Gly Leu
65      70      75      80
Phe Cys Asp Phe Gly Ser Pro Ala Asn Arg Lys Ile Gly Val Cys Thr
85      90      95
Ala Lys Asp Gly Ala Pro Cys Ile Phe Gly Gly Thr Val Tyr Arg Ser
100     105     110
Gly Glu Ser Phe Gln Ser Ser Cys Lys Tyr Gln Cys Thr Cys Leu Asp
115     120     125
Gly Ala Val Gly Cys Met Pro Leu Cys Ser Met Asp Val Arg Leu Pro
130     135     140
Ser Pro Asp Cys Pro Phe Pro Arg Arg Val Lys Leu Pro Gly Lys Cys
145     150     155     160
Cys Glu Glu Trp Val Cys Asp Glu Pro Lys Asp Gln Thr Val Val Gly
165     170     175
Pro Ala Leu Ala Ala Tyr Arg Leu Glu Asp Thr Phe Gly Pro Asp Pro
180     185     190
Thr Met Ile Arg Ala Asn Cys Leu Val Gln Thr Thr Glu Trp Ser Ala
195     200     205
Cys Ser Lys Thr Cys Gly Met Gly Ile Ser Thr Arg Val Thr Asn Asp
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Asn Ala Ser Cys Arg Leu Glu Lys Gln Ser Arg Leu Cys Met Val Arg
225     230     235     240
Pro Cys Glu Ala Asp Leu Glu Glu Asn Ile Lys Lys Gly Lys Lys Cys
245     250     255
Ile Arg Thr Pro Lys Ile Ser Lys Pro Ile Lys Phe Glu Leu Ser Gly
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Cys Thr Ser Met Lys Thr Tyr Arg Ala Lys Phe Cys Gly Val Cys Thr
275     280     285
Asp Gly Arg Cys Cys Thr Pro His Arg Thr Thr Thr Leu Pro Val Glu
290     295     300
Phe Lys Cys Pro Asp Gly Glu Val Met Lys Lys Asn Met Met Phe Ile
305     310     315     320
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Glu Ser Leu Tyr Tyr Arg Lys Met Tyr Gly Asp Met Ala
340     345

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<210> 47
 <211> 3025
 <212> DNA
 <213> Homo sapiens

<400> 47
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<210> 48

<211> 752
 <212> PRT
 <213> Homo sapiens

<400> 48

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			20					25					30		
Lys	Leu	Ala	Leu	Ala	Glu	Ala	Arg	Val	Gln	Glu	Glu	Glu	Gln	Lys	Ala
		35					40					45			
Thr	Arg	Leu	Glu	Lys	Glu	Leu	Gln	Thr	Gln	Thr	Thr	Lys	Phe	His	Gln
	50					55						60			
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65					70					75					80
Arg	Gln	Leu	Gln	Gln	Lys	Leu	Ala	Ala	Leu	Ser	Arg	Gln	Ile	Asp	Glu
				85					90					95	
Leu	Glu	Glu	Thr	Asn	Arg	Ser	Leu	Arg	Lys	Ala	Glu	Glu	Glu	Leu	Gln
			100					105					110		
Asp	Ile	Lys	Glu	Lys	Ile	Ser	Lys	Gly	Glu	Tyr	Gly	Asn	Ala	Gly	Ile
		115					120					125			
Met	Ala	Glu	Val	Glu	Glu	Leu	Ile	Lys	Met	Glu	Glu	Gln	Cys	Arg	Asp
	130					135						140			
Leu	Asn	Lys	Arg	Leu	Glu	Arg	Glu	Thr	Leu	Gln	Ser	Lys	Asp	Phe	Lys
145					150					155					160
Leu	Glu	Val	Glu	Lys	Leu	Ser	Lys	Arg	Ile	Met	Ala	Leu	Glu	Lys	Leu
				165					170					175	
Glu	Asp	Ala	Phe	Asn	Lys	Ser	Lys	Gln	Glu	Cys	Tyr	Ser	Leu	Lys	Cys
			180					185					190		
Asn	Leu	Glu	Lys	Glu	Arg	Met	Thr	Thr	Lys	Gln	Leu	Ser	Gln	Glu	Leu
		195					200						205		
Glu	Ser	Leu	Lys	Val	Arg	Ile	Lys	Glu	Leu	Glu	Ala	Ile	Glu	Ser	Arg
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Leu	Glu	Lys	Thr	Glu	Phe	Thr	Leu	Lys	Glu	Asp	Leu	Thr	Lys	Leu	Lys
225					230					235					240
Thr	Leu	Thr	Val	Met	Phe	Val	Asp	Glu	Arg	Lys	Thr	Met	Ser	Glu	Lys
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Leu	Lys	Lys	Thr	Glu	Asp	Lys	Leu	Gln	Ala	Ala	Ser	Ser	Gln	Leu	Gln
			260					265					270		
Val	Glu	Gln	Asn	Lys	Val	Thr	Thr	Val	Thr	Glu	Lys	Leu	Ile	Glu	Glu
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Thr	Lys	Arg	Ala	Leu	Lys	Ser	Lys	Thr	Asp	Val	Glu	Glu	Lys	Met	Tyr
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Ser	Val	Thr	Lys	Glu	Arg	Asp	Asp	Leu	Lys	Asn	Lys	Leu	Lys	Ala	Glu
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Leu	Lys	Asp	Met	Lys	Ala	Ile	Glu	Asp	Asp	Leu	Met	Lys	Thr	Glu	Asp
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Glu	Tyr	Glu	Thr	Leu	Glu	Arg	Arg	Tyr	Ala	Asn	Glu	Arg	Asp	Lys	Ala
				405					410					415	
Gln	Phe	Leu	Ser	Lys	Glu	Leu	Glu	His	Val	Lys	Met	Glu	Leu	Ala	Lys
			420					425					430		

Tyr	Lys	Leu	Ala	Glu	Lys	Thr	Glu	Thr	Ser	His	Glu	Gln	Trp	Leu	Phe
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Lys	Arg	Leu	Gln	Glu	Glu	Glu	Ala	Lys	Ser	Gly	His	Leu	Ser	Arg	Glu
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Val	Asp	Ala	Leu	Lys	Glu	Lys	Ile	His	Glu	Tyr	Met	Ala	Thr	Glu	Asp
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Leu	Ile	Cys	His	Leu	Gln	Gly	Asp	His	Ser	Val	Cys	Lys	Lys	Lys	Leu
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Pro	Ser	Leu	Asn	Gly	Arg	Arg	Ile	Ser	Asp	Pro	Gln	Val	Phe	Ser	Lys
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Glu	Val	Gln	Thr	Glu	Ala	Val	Asp	Asn	Glu	Pro	Pro	Asp	Tyr	Lys	Ser
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Leu	Ile	Pro	Leu	Glu	Arg	Ala	Val	Ile	Asn	Gly	Gln	Leu	Tyr	Glu	Glu
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Ser	Glu	Asn	Gln	Asp	Glu	Asp	Pro	Asn	Asp	Glu	Gly	Ser	Val	Leu	Ser
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Phe	Lys	Cys	Ser	Gln	Ser	Thr	Pro	Cys	Pro	Val	Asn	Arg	Lys	Leu	Trp
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Ile	Pro	Trp	Met	Lys	Ser	Lys	Glu	Gly	His	Leu	Gln	Asn	Gly	Lys	Met
		610				615					620				
Gln	Thr	Lys	Pro	Asn	Ala	Asn	Phe	Val	Gln	Pro	Gly	Asp	Leu	Val	Leu
					630					635					640
Ser	His	Thr	Pro	Gly	Gln	Pro	Leu	His	Ile	Lys	Val	Thr	Pro	Asp	His
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Val	Gln	Asn	Thr	Ala	Thr	Leu	Glu	Ile	Thr	Ser	Pro	Thr	Thr	Glu	Ser
			660				665							670	
Pro	His	Ser	Tyr	Thr	Ser	Thr	Ala	Val	Ile	Pro	Asn	Cys	Gly	Thr	Pro
		675					680					685			
Lys	Gln	Arg	Ile	Thr	Ile	Leu	Gln	Asn	Ala	Ser	Ile	Thr	Pro	Val	Lys
		690				695					700				
Ser	Lys	Thr	Ser	Thr	Glu	Asp	Leu	Met	Asn	Leu	Glu	Gln	Gly	Met	Ser
					710					715					720
Pro	Ile	Thr	Met	Ala	Thr	Phe	Ala	Arg	Ala	Gln	Thr	Pro	Glu	Ser	Cys
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Gly	Ser	Leu	Thr	Pro	Glu	Arg	Thr	Met	Ser	Leu	Phe	Arg	Phe	Trp	Leu
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<210> 49

<211> 1480

<212> DNA

<213> Homo sapiens

<400> 49

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acatagcatc ggtcacagtg ctgccccacg cctcttccca cttgcctgga ctgtgctgct 660

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<210> 50

<211> 205

<212> PRT

<213> Homo sapiens

<400> 50

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Arg Asn Glu Asp Tyr Thr Ile His Val Gln Leu Asn Asp Tyr Val Asp
          35          40          45
Ile Ile Cys Pro His Tyr Glu Asp His Ser Val Ala Asp Ala Ala Met
          50          55          60
Glu Gln Tyr Ile Leu Tyr Leu Val Glu His Glu Glu Tyr Gln Leu Cys
          65          70          75          80
Gln Pro Gln Ser Lys Asp Gln Val Arg Trp Gln Cys Asn Arg Pro Ser
          85          90          95
Ala Lys His Gly Pro Glu Lys Leu Ser Glu Lys Phe Gln Arg Phe Thr
          100          105          110
Pro Phe Thr Leu Gly Lys Glu Phe Lys Glu Gly His Ser Tyr Tyr Tyr
          115          120          125
Ile Ser Lys Pro Ile His Gln His Glu Asp Arg Cys Leu Arg Leu Lys
          130          135          140
Val Thr Val Ser Gly Lys Ile Thr His Ser Pro Gln Ala His Val Asn
          145          150          155          160
Pro Gln Glu Lys Arg Leu Ala Ala Asp Asp Pro Glu Val Arg Val Leu
          165          170          175
His Ser Ile Gly His Ser Ala Ala Pro Arg Leu Phe Pro Leu Ala Trp
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Thr Val Leu Leu Leu Pro Leu Leu Leu Leu Gln Thr Pro
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<210> 51

<211> 15952

<212> DNA

<213> Homo sapiens

<400> 51

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caggccccag gccaggagca tagctggggg gtatgtggag gcctcggggc aggcccagag 180
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Thr	Gly	Leu	Tyr	Met	Leu	Gln	Leu	Ala	Gly	Arg	Gly	Ser	Ala	Val	His
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Gln	Leu	Ser	Glu	Glu	Leu	Arg	Cys	Ala	Leu	Arg	Asp	Ala	Arg	Val	Thr
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Pro	Gly	Ser	Gly	Ala	Leu	Gln	Gly	Gln	Ser	Val	Ser	Val	Trp	Glu	Leu
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Ala	Gly	Ser	Pro	Arg	Pro	Asp	Pro	Arg	Glu	Ala	Leu	Arg	Ala	Ala	Thr
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Pro	Gln	Leu	Gln	Asp	Ala	Arg	Arg	Gly	Pro	Arg	Glu	Pro	Gly	Pro	Ala

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 gatggacctg gtttaataat ggaagaacag cacaagtgtt cttcgaagag ccttgaacat 360
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<210> 54
 <211> 313
 <212> PRT
 <213> Homo sapiens

<400> 54

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          20          25          30
Thr Glu Phe Pro Glu Leu Ala Pro Ser Gln Asn Gln Asn His Leu Lys
          35          40          45
Asp Trp Phe Leu Glu Asn Lys Ser Glu Val Cys Glu Cys Arg Asn Asn
 50          55          60
Glu Asp Gly Pro Gly Leu Ile Met Glu Glu Gln His Lys Cys Ser Ser
 65          70          75          80
Lys Ser Leu Glu His Lys Thr Gln Thr Pro Pro Val Glu Glu Asn Val
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Thr Gln Lys Ile Ser Asp Leu Glu Ile Cys Ala Asp Glu Phe Pro Gly
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Ser Glu Tyr Asp Pro Ser Arg Cys Phe Ala Phe Val His Asp Leu Cys
          165          170          175
Asp Glu Glu Lys Ser Tyr Pro Val Pro Lys Gly Ser Leu Asp Ile Ile
          180          185          190
Ile Leu Ile Phe Val Leu Ser Ala Ile Val Pro Asp Lys Met Gln Lys
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Ala Ile Asn Arg Leu Ser Arg Leu Leu Lys Pro Gly Gly Met Val Leu
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Leu Arg Asp Tyr Gly Arg Tyr Asp Met Ala Gln Leu Arg Phe Lys Lys
          225          230          235          240
Gly Gln Cys Leu Ser Gly Asn Phe Tyr Val Arg Gly Asp Gly Thr Arg
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Val Tyr Phe Phe Thr Gln Glu Glu Leu Asp Thr Leu Phe Thr Thr Ala
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Gly Leu Glu Lys Val Gln Asn Leu Val Asp Arg Arg Leu Gln Val Asn
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<210> 55

<211> 3334

<212> DNA

<213> Homo sapiens

<400> 55

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<210> 56
 <211> 509
 <212> PRT
 <213> Homo sapiens

<400> 56
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				85						90				95	
Val	Lys	Gln	Phe	Gln	Asn	Val	Gln	Gln	Val	Glu	Tyr	Ser	Ser	Ile	Arg
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Gly	Phe	Leu	Ser	Lys	His	Ser	Ser	Asp	Gly	Leu	Arg	Gln	Leu	Leu	His
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Asp	Leu	Asp	Leu	Asp	Thr	Glu	Phe	Glu	Ile	Leu	Leu	Pro	Arg	Arg	Arg
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			180					185						190	
His	Asn	Glu	Ile	Val	Tyr	Ala	Val	Glu	Lys	Leu	Ser	Lys	Glu	Asn	Asn
	195						200							205	
Ser	Tyr	Ser	Val	Asp	Ala	Ala	Glu	Val	Thr	Glu	Leu	His	Val	Ile	Ser
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Lys	Ile	Gln	Arg	Gln	Ile	Val	Ser	Arg	Phe	Leu	Gln	Gly	Lys	Pro	Arg
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Gln	Asp	Ile	Leu	Gln	Met	Gly	Asp	Gln	Thr	Ile	His	Val	Leu	Lys	Ala
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Ser	Ala	His	Lys	Ser	Glu	Gln	Leu	Leu	Arg	Leu	His	Lys	Glu	Pro	Phe
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Gly	Glu	Ile	Ser	Ser	Arg	Tyr	Lys	Ala	Asp	Leu	Ser	Pro	Glu	Asn	Ala
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Lys	Leu	Leu	Ser	Thr	Phe	Leu	Asn	Gln	Thr	Gly	Leu	Asp	Ala	Phe	Leu
			420					425						430	
Leu	Glu	Leu	His	Glu	Met	Ile	Ile	Leu	Lys	Leu	Lys	Asn	Pro	Gln	Thr
	435					440						445			
Gln	Thr	Glu	Glu	Arg	Phe	Arg	Pro	Gln	Trp	Ser	Leu	Arg	Asp	Thr	Leu
	450					455					460				
Val	Ser	Tyr	Met	Gln	Thr	Lys	Glu	Ser	Glu	Ile	Leu	Pro	Glu	Met	Ala
465					470					475					480
Ser	Gln	Phe	Pro	Glu	Glu	Ile	Leu	Leu	Ala	Ser	Cys	Val	Ser	Val	Trp
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<210> 57
 <211> 1760
 <212> DNA
 <213> Homo sapiens

<400> 57

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<210> 58
 <211> 232
 <212> PRT
 <213> Homo sapiens

<400> 58

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  20          25          30
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  35          40          45
Leu Glu Ser Ser Asp Cys Glu Ser Leu Asp Ser Ser Asn Ser Gly Phe
  50          55          60
Gly Pro Glu Glu Asp Thr Ala Tyr Leu Asp Gly Val Ser Leu Pro Asp
  65          70          75          80
Phe Glu Leu Leu Ser Asp Pro Glu Asp Glu His Leu Cys Ala Asn Leu
  85          90          95
Met Gln Leu Leu Gln Glu Ser Leu Ala Gln Ala Arg Leu Gly Ser Arg
  100          105          110
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Ala	Leu	Leu	Asp	Val	Cys	Val	Glu	Gln	Gly	Lys	Ser	Cys	His	Ser	Val
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Gly	Gln	Leu	Ala	Leu	Asp	Pro	Ser	Leu	Val	Pro	Thr	Phe	Gln	Leu	Thr
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Leu	Val	Leu	Arg	Leu	Asp	Ser	Arg	Leu	Trp	Pro	Lys	Ile	Gln	Gly	Leu
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<210> 59

<211> 2012

<212> DNA

<213> Homo sapiens

<400> 59

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aaaaaaaaaa	aaaaaaaaaa	aaaaaaaaaa	aa			2012

<210> 60
 <211> 495
 <212> PRT
 <213> Homo sapiens

<400> 60

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			20					25					30		
Arg	Val	Arg	Ala	Leu	Asn	Asp	Gly	Gly	Tyr	Gly	Pro	Tyr	Ser	Asp	Val
		35					40					45			
Ser	Glu	Ile	Thr	Thr	Ala	Ala	Gly	Pro	Pro	Gly	Gln	Cys	Lys	Ala	Pro
	50					55					60				
Cys	Ile	Ser	Cys	Thr	Pro	Asp	Gly	Cys	Val	Leu	Val	Gly	Trp	Glu	Ser
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<212> PRT

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<212> DNA

<213> Homo sapiens

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<212> PRT

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<222> 779

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 <212> PRT
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<400> 69
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<210> 71

<211> 338

<212> PRT

<213> Homo sapiens

<400> 71

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      20      25      30
Gly Val Asn Asp Ser Phe Pro Asp Gly Asp Tyr Asp Ala Asn Leu Glu
      35      40      45
Ala Ala Ala Pro Cys His Ser Cys Asn Leu Leu Asp Asp Ser Ala Leu
      50      55      60
Pro Phe Phe Ile Leu Thr Ser Val Leu Gly Ile Leu Ala Ser Ser Thr
      65      70      75      80
Val Leu Phe Met Leu Phe Arg Pro Leu Phe Arg Trp Gln Leu Cys Pro
      85      90      95
Gly Trp Pro Val Leu Ala Gln Leu Ala Val Gly Ser Ala Leu Phe Ser
      100      105      110
Ile Val Val Pro Val Leu Ala Pro Gly Leu Gly Ser Thr Arg Ser Ser
      115      120      125
Ala Leu Cys Ser Leu Gly Tyr Cys Val Trp Tyr Gly Ser Ala Phe Ala
      130      135      140
Gln Ala Leu Leu Leu Gly Cys His Ala Ser Leu Gly His Arg Leu Gly
      145      150      155      160
Ala Gly Gln Val Pro Gly Leu Thr Leu Gly Leu Thr Val Gly Ile Trp
      165      170      175
Gly Val Ala Ala Leu Leu Thr Leu Pro Val Thr Leu Ala Ser Gly Ala
      180      185      190
Ser Gly Gly Leu Cys Thr Leu Ile Tyr Ser Thr Glu Leu Lys Ala Leu
      195      200      205
Gln Ala Thr His Thr Val Ala Cys Leu Ala Ile Phe Val Leu Leu Pro
      210      215      220
Leu Gly Leu Phe Gly Ala Lys Gly Leu Lys Lys Ala Leu Gly Met Gly
      225      230      235      240

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<210> 72
<211> 817
<212> DNA
<213> Homo sapiens
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<400> 72						
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actgcagcct	ccaactccta	gcctcaagtg	atcctcctgt	ctcaacctcc	caagtaggat	720
tacaagcatg	cgccgacgat	gcccagaatc	cagaactttg	tctatcactc	tccccaacaa	780
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<210> 73
<211> 130
<212> PRT
<213> Homo sapiens
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<400> 73															
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Thr	Cys	Ser	Gly	Val	Glu	Ala	Gly	Lys	Lys	Lys	Cys	Ser	Glu	Ser	Ser
			20					25					30		
Asp	Ser	Gly	Ser	Gly	Phe	Trp	Lys	Ala	Leu	Thr	Phe	Met	Ala	Val	Gly
		35					40					45			
Gly	Gly	Leu	Ala	Val	Ala	Gly	Leu	Pro	Ala	Leu	Gly	Phe	Thr	Gly	Ala
	50					55					60				
Gly	Ile	Ala	Ala	Asn	Ser	Val	Ala	Ala	Ser	Leu	Met	Ser	Trp	Ser	Ala
65					70					75					80
Ile	Leu	Asn	Gly	Gly	Gly	Val	Pro	Ala	Gly	Gly	Leu	Val	Ala	Thr	Leu
				85					90					95	
Gln	Ser	Leu	Gly	Ala	Gly	Gly	Ser	Ser	Val	Val	Ile	Gly	Asn	Ile	Gly
			100				105						110		
Ala	Leu	Met	Gly	Tyr	Ala	Thr	His	Lys	Tyr	Leu	Asp	Ser	Glu	Glu	Asp
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Glu Glu
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<210> 74
<211> 2861
<212> DNA
<213> Homo sapiens

<400> 74

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<210> 75
 <211> 187
 <212> PRT
 <213> Homo sapiens

<400> 75
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 35 40 45
 Arg Glu Ile Val Ala Leu Lys Thr Lys Leu Lys Glu Cys Glu Ala Ser
 50 55 60
 Lys Asp Gln Asn Thr Pro Val Val His Pro Pro Pro Thr Pro Gly Ser
 65 70 75 80
 Cys Gly His Gly Gly Val Val Asn Ile Ser Lys Pro Ser Val Val Gln
 85 90 95
 Leu Asn Trp Arg Gly Phe Ser Tyr Leu Tyr Gly Ala Trp Gly Arg Asp
 100 105 110
 Tyr Ser Pro Gln His Pro Asn Lys Gly Leu Tyr Trp Val Ala Pro Leu
 115 120 125
 Asn Thr Asp Gly Arg Leu Leu Glu Tyr Tyr Ile Leu Tyr Asn Thr Leu
 130 135 140
 Asp Asp Leu Leu Leu Tyr Ile Asn Ala Arg Glu Leu Arg Ile Thr Tyr
 145 150 155 160
 Gly Gln Gly Ser Gly Thr Ala Val Tyr Asn Asn Asn Met Tyr Val Asn
 165 170 175
 Met Tyr Thr Pro Gly Ile Leu Pro Glu Leu Thr
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<210> 76
 <211> 956
 <212> DNA
 <213> Homo sapiens

<400> 76
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 aacctggcgg agacagagaa ccgctactgc gtgcagctgt cccagatcca ggggctgatt 540
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<210> 77
 <211> 266
 <212> PRT
 <213> Homo sapiens

<400> 77

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 20 25 30
 Leu Ala Arg Ala Asp Leu Glu Met Gln Ile Glu Asn Leu Lys Glu Glu
 35 40 45
 Leu Ala Tyr Leu Lys Lys Asn His Glu Glu Glu Met Asn Ala Leu Arg
 50 55 60
 Gly Gln Val Gly Gly Glu Ile Asn Val Glu Met Asp Ala Ala Pro Gly
 65 70 75 80
 Val Asp Leu Ser Arg Ile Leu Asn Glu Met Arg Asp Gln Tyr Glu Lys
 85 90 95
 Met Ala Glu Lys Asn Arg Lys Asp Ala Glu Asp Trp Phe Phe Ser Lys
 100 105 110
 Thr Glu Glu Leu Asn Arg Glu Val Ala Thr Asn Ser Glu Leu Val Gln
 115 120 125
 Ser Gly Lys Ser Glu Ile Ser Glu Leu Arg Arg Thr Met Gln Ala Leu
 130 135 140
 Glu Ile Glu Leu Gln Ser Gln Leu Ser Met Lys Ala Ser Leu Glu Gly
 145 150 155 160
 Asn Leu Ala Glu Thr Glu Asn Arg Tyr Cys Val Gln Leu Ser Gln Ile
 165 170 175
 Gln Gly Leu Ile Gly Ser Val Glu Glu Gln Leu Ala Gln Leu Arg Cys
 180 185 190
 Glu Met Glu Gln Gln Asn Gln Glu Tyr Lys Ile Leu Leu Asp Val Lys
 195 200 205
 Thr Arg Leu Glu Gln Glu Ile Ala Thr Tyr Arg Arg Leu Leu Glu Gly
 210 215 220
 Glu Asp Ala His Leu Thr Gln Tyr Lys Lys Glu Pro Val Thr Thr Arg
 225 230 235 240
 Gln Val Arg Thr Ile Val Glu Glu Val Gln Asp Gly Lys Val Ile Ser
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 Ser Arg Glu Gln Val His Gln Thr Thr Arg
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<210> 78

<211> 1689

<212> DNA

<213> Homo sapiens

<400> 78

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<210> 79

<211> 373

<212> PRT

<213> Homo sapiens

<400> 79

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Ile Ser Ile Thr Glu Asn Val Leu His Phe Lys Ala Gln Gly His Gly
 35          40          45
Ala Lys Gly Asp Asn Val Tyr Glu Phe His Leu Glu Phe Leu Asp Leu
 50          55          60
Val Lys Pro Glu Pro Val Tyr Lys Leu Thr Gln Arg Gln Val Asn Ile
 65          70          75          80
Thr Val Gln Lys Lys Val Ser Gln Trp Trp Glu Arg Leu Thr Lys Gln
 85          90          95
Glu Lys Arg Pro Leu Phe Leu Ala Pro Asp Phe Asp Arg Trp Leu Asp
100          105          110
Glu Ser Asp Ala Glu Met Glu Leu Arg Ala Lys Glu Glu Glu Arg Leu
115          120          125
Asn Lys Leu Arg Leu Glu Ser Glu Gly Ser Pro Glu Thr Leu Thr Asn
130          135          140
Leu Arg Lys Gly Tyr Leu Phe Met Tyr Asn Leu Val Gln Phe Leu Gly
145          150          155          160
Phe Ser Trp Ile Phe Val Asn Leu Thr Val Arg Phe Cys Ile Leu Gly
165          170          175
Lys Glu Ser Phe Tyr Asp Thr Phe His Thr Val Ala Asp Met Met Tyr
180          185          190
Phe Cys Gln Met Leu Ala Val Val Glu Thr Ile Asn Ala Ala Ile Gly
195          200          205
Val Thr Thr Ser Pro Val Leu Pro Ser Leu Ile Gln Leu Leu Gly Arg
210          215          220
Asn Phe Ile Leu Phe Ile Ile Phe Gly Thr Met Glu Glu Met Gln Asn
225          230          235          240
Lys Ala Val Val Phe Phe Val Phe Tyr Leu Trp Ser Ala Ile Glu Ile
245          250          255
Phe Arg Tyr Ser Phe Tyr Met Leu Thr Cys Ile Asp Met Asp Trp Lys
260          265          270
Val Leu Thr Trp Leu Arg Tyr Thr Leu Trp Ile Pro Leu Tyr Pro Leu
275          280          285
Gly Cys Leu Val Glu Ala Val Ser Val Ile Gln Ser Ile Pro Ile Phe
290          295          300

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Asn Glu Thr Gly Arg Phe Ser Phe Thr Leu Pro Tyr Pro Val Lys Ile
 305 310 315 320
 Lys Val Arg Phe Ser Phe Phe Leu Gln Ile Tyr Leu Ile Met Ile Phe
 325 330 335
 Leu Gly Leu Tyr Ile Asn Phe Arg His Leu Tyr Lys Gln Arg Arg Arg
 340 345 350
 Arg Tyr Gly Lys Lys Arg Lys Arg Ser Thr Lys Lys Lys Asp Leu Asp
 355 360 365
 Gly Phe Leu Pro Val
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<210> 80
 <211> 1824
 <212> DNA
 <213> Homo sapiens

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Glu	Val	Ser	Asn	Thr	Lys	Ser	Ser	Ser	Gln	Ile	Pro	Ala	Gln	Pro	Ser
370						375					380				
Val	Ala	Lys	Val	Pro	Tyr	Gly	Lys	Gly	Pro	Ser	Phe	Asn	Gln	Glu	Arg
385					390					395					400
Gly	Thr	Ser	Ser	His	Leu	Pro	Pro	Pro	Pro	Lys	Leu	Leu	Ala	Gln	Gln
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His	Pro	Pro	Pro	Asp	Arg	Gln	Ala	Val	Pro	Gly	Arg	Pro	Gly	Pro	Phe
			420					425					430		
Pro	Ser	Lys	Gln	Gln	Val	Ala	Asp	Glu	Asp	Glu	Ile	Trp	Lys	Gln	Arg
		435				440						445			
Arg	Arg	Gln	Gln	Ser	Glu	Ile	Ser	Ala	Ala	Val	Glu	Arg	Ala	Arg	Lys
450						455					460				
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Cys	Ala	Glu	Lys	Leu	Lys	Arg	Leu	Asp	Glu	Lys	Leu	Gly	Ile	Leu	Glu
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Lys	Gln	Pro	Ser	Pro	Glu	Glu	Ile	Arg	Glu	Arg	Glu	Arg	Glu	Lys	Glu
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Arg	Glu	Arg	Glu	Lys	Glu	Leu	Glu	Lys	Glu	Gln	Glu	Gln	Glu	Arg	Glu
		515					520					525			
Lys	Glu	Arg	Glu	Lys	Asp	Arg	Glu	Arg	Gln	Gln	Glu	Lys	Glu	Lys	Glu
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Gln	Glu	Lys	Glu	Lys	Glu	Leu	Glu	Arg	Gln	Lys	Glu	Lys	Glu	Lys	Glu
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Thr	Pro	Val	Val	His	Glu	Thr	Glu	Pro	Glu	Ser	Gly	Ser	Gln	Pro	Arg
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Pro	Ala	Val	Leu	Ser	Gly	Tyr	Phe	Lys	Gln	Phe	Gln	Lys	Ser	Leu	Pro
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		675					680					685			
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690						695					700				
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Met	Gln	Pro	His	Pro	Gln	His	Leu	Ala	Ser	Met	Gly	Phe	Asp	Pro	Arg
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Trp	Leu	Met	Met	Gln	Ser	Tyr	Met	Asp	Pro	Arg	Met	Met	Ser	Gly	Arg
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Pro	Ala	Met	Asp	Ile	Pro	Pro	Ile	His	Pro	Gly	Met	Ile	Pro	Pro	Lys

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Pro Leu Met Arg Arg Asp Gln Met Glu Gly Ser Pro Asn Ser Ser Glu		
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Ser Phe Glu His Ile Ala Arg Ser Ala Arg Asp His Ala Ile Ser Leu		
785	790	795
Ser Glu Pro Arg Met Leu Trp Gly Ser Asp Pro Tyr Pro His Ala Glu		
805	810	815
Pro Gln Gln Ala Thr Thr Pro Lys Ala Thr Glu Glu Pro Glu Asp Val		
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Arg Ser Glu Ala Ala Leu Asp Gln Glu Gln Ile Thr Ala Ala Tyr Ser		
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Val Glu His Asn Gln Leu Glu Ala His Pro Lys Ala Asp Phe Ile Arg		
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Glu Ser Ser Glu Ala Gln Val Gln Lys Phe Leu Ser Arg Ser Val Glu		
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Asp Val Arg Pro His His Thr Asp Ala Asn Asn Gln Ser Ala Cys Phe		
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Glu Ala Pro Asp Gln Lys Thr Leu Ser Ala Pro Gln Glu Glu Arg Ile		
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Ser Ala Val Glu Ser Gln Pro Ser Arg Lys Arg Ser Val Ser His Gly		
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Ser Asn His Thr Gln Lys Pro Asp Glu Gln Arg Ser Glu Pro Ser Ala		
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Gly Ile Pro Lys Val Thr Ser Arg Cys Ile Asp Ser Lys Glu Pro Ile		
945	950	955
Glu Arg Pro Glu Glu Lys Pro Lys Lys Glu Gly Phe Ile Arg Ser Ser		
965	970	975
Glu Gly Pro Lys Pro Glu Lys Val Tyr Lys Ser Lys Ser Glu Thr Arg		
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Trp Gly Pro Arg Pro Ser Ser Asn Arg Arg Glu Glu Val Asn Asp Arg		
995	1000	1005
Pro Val Arg Arg Ser Gly Pro Ile Lys Lys Pro Val Leu Arg Asp Met		
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Lys Glu Glu Arg Glu Gln Arg Lys Glu Lys Glu Gly Glu Lys Ala Glu		
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Lys Val Thr Glu Lys Val Val Val Lys Pro Glu Lys Thr Glu Lys Lys		
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Asp Leu Pro Pro Pro Pro Pro Pro Pro Gln Pro Pro Ala Pro Ile Gln		
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Pro Gln Ser Val Pro Pro Pro Ile Gln Pro Glu Ala Glu Lys Phe Pro		
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Ser Thr Glu Thr Ala Thr Leu Ala Gln Lys Pro Ser Gln Asp Thr Glu		
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Lys Pro Leu Glu Pro Val Ser Thr Val Gln Val Glu Pro Ala Val Lys		
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Thr Val Asn Gln Gln Thr Met Ala Ala Pro Val Val Lys Glu Glu Lys		
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Gln Pro Glu Lys Val Ile Ser Lys Asp Leu Val Ile Glu Arg Pro Arg		
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Pro Asp Ser Arg Pro Ala Val Lys Lys Glu Ser Thr Leu Pro Pro Arg		
1155	1160	1165
Thr Tyr Trp Lys Glu Ala Arg Glu Arg Asp Trp Phe Pro Asp Gln Gly		
1170	1175	1180
Tyr Arg Gly Arg Gly Arg Gly Glu Tyr Tyr Ser Arg Gly Arg Ser Tyr		
1185	1190	1195
Arg Gly Ser Tyr Gly Gly Arg Gly Arg Gly Gly Arg Gly His Thr Arg		
1205	1210	1215
Asp Tyr Pro Gln Tyr Arg Asp Asn Lys Pro Arg Ala Glu His Ile Pro		
1220	1225	1230

Ser Gly Pro Leu Arg Gln Arg Glu Glu Ser Glu Thr Arg Ser Glu Ser	1235	1240	1245
Ser Asp Phe Glu Val Val Pro Lys Arg Arg Arg Gln Arg Gly Ser Glu	1250	1255	1260
Thr Asp Thr Asp Ser Glu Ile His Glu Ser Ala Ser Asp Lys Asp Ser	1265	1270	1275
Leu Ser Lys Gly Lys Leu Pro Lys Arg Glu Glu Arg Pro Glu Asn Lys	1285	1290	1295
Lys Pro Val Lys Pro His Ser Ser Phe Lys Pro Asp Asn His Val Arg	1300	1305	1310
Ile Asp Asn Arg Leu Leu Glu Lys Pro Tyr Val Arg Asp Asp Asp Lys	1315	1320	1325
Ala Lys Pro Gly Phe Leu Pro Lys Gly Glu Pro Thr Arg Arg Gly Arg	1330	1335	1340
Gly Gly Thr Phe Arg Arg Gly Gly Arg Asp Pro Gly Gly Arg Pro Ser	1345	1350	1355
Arg Pro Ser Thr Leu Arg Arg Pro Ala Tyr Arg Asp Asn Gln Trp Asn	1365	1370	1375
Pro Arg Gln Ser Glu Val Pro Lys Pro Glu Asp Gly Glu Pro Pro Arg	1380	1385	1390
Arg His Glu Gln Phe Ile Pro Ile Ala Ala Asp Lys Arg Pro Pro Lys	1395	1400	1405
Phe Glu Arg Lys Phe Asp Pro Ala Arg Glu Arg Pro Arg Arg Gln Arg	1410	1415	1420
Pro Thr Arg Pro Pro Arg Gln Asp Lys Pro Pro Arg Phe Arg Arg Leu	1425	1430	1435
Arg Glu Arg Glu Ala Ala Ser Lys Ser Asn Glu Val Val Ala Val Pro	1445	1450	1455
Thr Asn Gly Thr Val Asn Asn Val Ala Gln Glu Pro Val Asn Thr Leu	1460	1465	1470
Gly Asp Ile Ser Gly Asn Lys Thr Pro Asp Leu Ser Asn Gln Asn Ser	1475	1480	1485
Ser Asp Gln Ala Asn Glu Glu Trp Glu Thr Ala Ser Glu Ser Ser Asp	1490	1495	1500
Phe Asn Glu Arg Arg Glu Arg Asp Glu Lys Lys Asn Ala Asp Leu Asn	1505	1510	1515
Ala Gln Thr Val Val Lys Val Gly Glu Asn Val Leu Pro Pro Lys Arg	1525	1530	1535
Glu Ile Ala Lys Arg Ser Phe Ser Ser Gln Arg Pro Val Asp Arg Gln	1540	1545	1550
Asn Arg Arg Gly Asn Asn Gly Pro Pro Lys Ser Gly Arg Asn Phe Ser	1555	1560	1565
Gly Pro Arg Asn Glu Arg Arg Ser Gly Pro Pro Ser Lys Ser Gly Lys	1570	1575	1580
Arg Gly Pro Phe Asp Asp Gln Pro Ala Gly Thr Thr Gly Val Asp Leu	1585	1590	1595
Ile Asn Gly Ser Ser Ala His His Gln Glu Gly Val Pro Asn Gly Thr	1605	1610	1615
Gly Gln Lys Asn Ser Lys Asp Ser Thr Gly Lys Lys Arg Glu Asp Pro	1620	1625	1630
Lys Pro Gly Pro Lys Lys Pro Lys Glu Lys Val Asp Ala Leu Ser Gln	1635	1640	1645
Phe Asp Leu Asn Asn Tyr Ala Ser Val Val Ile Ile Asp Asp His Pro	1650	1655	1660
Glu Val Thr Val Ile Glu Asp Pro Gln Ser Asn Leu Asn Asp Asp Gly	1665	1670	1675
Phe Thr Glu Val Val Ser Lys Lys Gln Gln Lys Arg Leu Gln Asp Glu	1685	1690	1695
Glu Arg Arg Lys Lys Glu Glu Gln Val Ile Gln Val Trp Asn Lys Lys			

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Asn	Ala	Asn	Glu	Lys	Gly	Arg	Ser	Gln	Thr	Ser	Lys	Leu	Pro	Pro	Arg	
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Phe	Ala	Lys	Lys	Gln	Ala	Thr	Gly	Ile	Gln	Gln	Ala	Gln	Ser	Ser	Ala	
		1730						1735				1740				
Ser	Val	Pro	Pro	Leu	Ala	Ser	Ala	Pro	Leu	Pro	Pro	Ser	Thr	Ser	Ala	
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Ser	Val	Pro	Ala	Ser	Thr	Ser	Ala	Pro	Leu	Pro	Ala	Thr	Leu	Thr	Pro	
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His	Lys	Pro	Val	Gln	Asn	Pro	Leu	Gln	Thr	Thr	Ser	Gln	Ser	Ser	Lys	
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Gln	Pro	Pro	Pro	Ser	Ile	Arg	Leu	Pro	Ser	Ala	Gln	Thr	Pro	Asn	Gly	
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Thr	Asp	Tyr	Val	Ala	Ser	Gly	Lys	Ser	Ile	Gln	Thr	Pro	Gln	Ser	His	
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Gly	Thr	Leu	Thr	Ala	Glu	Leu	Trp	Asp	Asn	Lys	Val	Ala	Pro	Pro	Ala	
1985					1990					1995					2000	
Val	Leu	Asn	Asp	Ile	Ser	Lys	Lys	Leu	Gly	Pro	Ile	Ser	Pro	Pro	Gln	
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			2020					2025					2030			
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Ala	Glu	Tyr	Gly	Thr	Asn	Ala	Lys	Glu	Ser	Val	Thr	Asp	Tyr	Thr	Thr	2180	2185	2190
Pro	Ser	Ser	Ser	Leu	Pro	Asn	Thr	Val	Ala	Thr	Asn	Asn	Thr	Lys	Met	2195	2200	2205
Glu	Asp	Thr	Leu	Val	Asn	Asn	Val	Pro	Leu	Pro	Asn	Thr	Leu	Pro	Leu	2210	2215	2220
Pro	Lys	Arg	Glu	Thr	Ile	Gln	Gln	Ser	Ser	Ser	Leu	Thr	Ser	Val	Pro	2225	2230	2235
Pro	Thr	Thr	Phe	Ser	Leu	Thr	Phe	Lys	Met	Glu	Ser	Ala	Arg	Lys	Ala	2245	2250	2255
Trp	Glu	Asn	Ser	Pro	Asn	Val	Arg	Glu	Lys	Gly	Ser	Pro	Val	Thr	Ser	2260	2265	2270
Thr	Ala	Pro	Pro	Ile	Ala	Thr	Gly	Val	Ser	Ser	Ser	Ala	Ser	Gly	Pro	2275	2280	2285
Ser	Thr	Ala	Asn	Tyr	Asn	Ser	Phe	Ser	Ser	Ala	Ser	Met	Pro	Gln	Ile	2290	2295	2300
Pro	Val	Ala	Ser	Val	Thr	Pro	Thr	Ala	Ser	Leu	Ser	Gly	Ala	Gly	Thr	2305	2310	2315
Tyr	Thr	Thr	Ser	Ser	Leu	Ser	Thr	Lys	Ser	Thr	Thr	Thr	Ser	Asp	Pro	2325	2330	2335
Pro	Asn	Ile	Cys	Lys	Val	Lys	Pro	Gln	Gln	Leu	Gln	Thr	Ser	Ser	Leu	2340	2345	2350
Pro	Ser	Ala	Ser	His	Phe	Ser	Gln	Leu	Ser	Cys	Met	Pro	Ser	Leu	Ile	2355	2360	2365
Ala	Gln	Gln	Gln	Gln	Asn	Pro	Gln	Val	Tyr	Val	Ser	Gln	Ser	Ala	Ala	2370	2375	2380
Ala	Gln	Ile	Pro	Ala	Phe	Tyr	Met	Asp	Thr	Ser	His	Leu	Phe	Asn	Thr	2385	2390	2395
Gln	His	Ala	Arg	Leu	Ala	Pro	Pro	Ser	Leu	Ala	Gln	Gln	Gln	Gly	Phe	2405	2410	2415
Gln	Pro	Gly	Leu	Ser	Gln	Pro	Thr	Ser	Val	Gln	Gln	Ile	Pro	Ile	Pro	2420	2425	2430
Ile	Tyr	Ala	Pro	Leu	Gln	Gly	Gln	His	Gln	Ala	Gln	Leu	Ser	Leu	Gly	2435	2440	2445
Ala	Gly	Pro	Ala	Val	Ser	Gln	Ala	Gln	Glu	Leu	Phe	Ser	Ser	Ser	Leu	2450	2455	2460
Gln	Pro	Tyr	Arg	Ser	Gln	Pro	Ala	Phe	Met	Gln	Ser	Ser	Leu	Ser	Gln	2465	2470	2475
Pro	Ser	Val	Val	Leu	Ser	Gly	Thr	Ala	Ile	His	Asn	Phe	Pro	Thr	Val	2485	2490	2495
Gln	His	Gln	Glu	Leu	Ala	Lys	Ala	Gln	Ser	Gly	Leu	Ala	Phe	Gln	Gln	2500	2505	2510
Thr	Ser	Asn	Thr	Gln	Pro	Ile	Pro	Ile	Leu	Tyr	Glu	His	Gln	Leu	Gly	2515	2520	2525
Gln	Ala	Ser	Gly	Leu	Gly	Gly	Ser	Gln	Leu	Ile	Asp	Thr	His	Leu	Leu	2530	2535	2540
Gln	Ala	Arg	Ala	Asn	Leu	Thr	Gln	Ala	Ser	Asn	Leu	Tyr	Ser	Gly	Gln	2545	2550	2555
Val	Gln	Gln	Pro	Gly	Gln	Thr	Asn	Phe	Tyr	Asn	Thr	Ala	Gln	Ser	Pro	2565	2570	2575
Ser	Ala	Leu	Gln	Gln	Val	Thr	Val	Pro	Leu	Pro	Ala	Ser	Gln	Leu	Ser	2580	2585	2590
Leu	Pro	Asn	Phe	Gly	Ser	Thr	Gly	Gln	Pro	Leu	Ile	Ala	Leu	Pro	Gln	2595	2600	2605
Thr	Leu	Gln	Pro	Pro	Leu	Gln	His	Thr	Thr	Pro	Gln	Ala	Gln	Ala	Gln	2610	2615	2620
Ser	Leu	Ser	Arg	Pro	Ala	Gln	Val	Ser	Gln	Pro	Phe	Arg	Gly	Leu	Ile	2625	2630	2635
Pro	Ala	Gly	Thr	Gln	His	Ser	Met	Ile	Ala	Thr	Thr	Gly	Lys	Met	Ser	2640		

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			2660						2665					2670					
Thr	Pro	Pro	Ile	Ala	Gly	Arg	Ser	Thr	Thr	Pro	Thr	Ser	Ser	Pro	Ser				
		2675					2680					2685							
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 <212> DNA
 <213> Homo sapiens

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 35 40 45
 Met Val Leu Ser Ala Met Gly Phe Thr Ala Ala Gly Ile Ala Ser Ser
 50 55 60
 Ser Ile Ala Ala Lys Met Met Ser Ala Ala Ala Ile Ala Asn Gly Gly
 65 70 75 80
 Gly Val Ala Ser Gly Ser Leu Val Gly Thr Leu Gln Ser Leu Gly Ala
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<210> 87

<211> 303

<212> PRT

<213> Homo sapiens

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Ala Ala Val Gln Ala Ser Pro Leu Gln Ala Leu Asp Phe Phe Gly Asn
          35          40          45
Gly Pro Pro Val Asn Tyr Lys Thr Gly Asn Leu Tyr Leu Arg Gly Pro
          50          55          60
Leu Lys Lys Ser Asn Ala Pro Leu Val Asn Val Thr Leu Tyr Tyr Glu
          65          70          75          80
Ala Leu Cys Gly Gly Cys Arg Ala Phe Leu Ile Arg Glu Leu Phe Pro
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Thr Trp Leu Leu Val Met Glu Ile Leu Asn Val Thr Ser Val Pro Tyr
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Gly Asn Ala Gln Glu Gln Asn Val Ser Gly Arg Trp Glu Phe Lys Cys
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Gln Leu Gly Glu Glu Glu Cys Lys Phe Asn Lys Val Glu Ala Cys Val
          130          135          140
Leu Asp Glu Leu Asp Met Glu Leu Ala Phe Leu Thr Met Ser Gly Met
          145          150          155          160
Ala Trp Lys Ser Leu Arg Thr Trp Arg Glu Val Cys His Tyr Ala Cys
          165          170          175
Ser Ser Thr Pro Gln Gly Cys Arg Gln Asn Tyr His Gly Val Cys Asn
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Gly Gly Pro Arg His Ala Ala His Ala Arg Gln Arg Pro Ala Asp Arg
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Cys Ser Pro Ala Thr Ala Arg Val Cys Ala Leu Gly His Arg Gln Trp
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Glu Thr Leu Gly Arg Ser Asp Pro Ala Pro Tyr Pro Cys Leu Pro Val
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Pro Glu Cys Leu Leu Arg Val Leu Ala Gly Gly Leu Arg Arg Ala His
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Gly Arg Arg Val Gly Thr Arg Leu Pro Ala Phe Phe Ser Asp Pro Asp
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290

295

300

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 <211> 905
 <212> DNA
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<210> 89
 <211> 132
 <212> PRT
 <213> Homo sapiens

<400> 89
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 35 40 45
 Ser Glu Thr Ser Val Pro Asp His Val Val Trp Ser Leu Phe Asn Thr
 50 55 60
 Leu Phe Met Asn Thr Cys Cys Leu Gly Phe Ile Ala Phe Ala Tyr Ser
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 Val Lys Ser Arg Asp Arg Lys Met Val Gly Asp Val Thr Gly Ala Gln
 85 90 95
 Ala Tyr Ala Ser Thr Ala Lys Cys Leu Asn Ile Trp Ala Leu Ile Leu
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 <211> 2499
 <212> DNA
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<210> 91

<211> 291

<212> PRT

<213> Homo sapiens

<400> 91

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      35             40             45
Ala Gln Cys Ala Pro Pro Pro Ala Val Cys Ala Glu Leu Val Arg Glu
      50             55             60
Pro Gly Cys Gly Cys Cys Leu Thr Cys Ala Leu Ser Glu Gly Gln Pro
      65             70             75             80
Cys Gly Ile Tyr Thr Glu Arg Cys Gly Ser Gly Leu Arg Cys Gln Pro

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<210> 92

<211> 1639

<212> DNA

<213> Homo sapiens

<400> 92

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<210> 93
 <211> 99
 <212> PRT
 <213> Homo sapiens

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 35 40 45
 Ile Lys Glu Leu Arg Val Ile Glu Ser Gly Pro His Cys Ala Asn Thr
 50 55 60
 Glu Ile Ile Val Lys Leu Ser Asp Gly Arg Glu Leu Cys Leu Asp Pro
 65 70 75 80
 Lys Glu Asn Trp Val Gln Arg Val Val Glu Lys Phe Leu Lys Arg Ala
 85 90 95
 Glu Asn Ser

<210> 94
 <211> 1840
 <212> DNA
 <213> Homo sapiens

<400> 94
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<210> 95
 <211> 426
 <212> PRT
 <213> Homo sapiens

<400> 95

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Pro	Asp	Cys	Pro	Ser	Cys	Ala	Leu	Ala	Ala	Leu	Pro	Lys	Asp	Val	Pro	35	40	45	
Asn	Ser	Gln	Pro	Glu	Met	Val	Glu	Ala	Val	Lys	Lys	His	Ile	Leu	Asn	50	55	60	
Met	Leu	His	Leu	Lys	Lys	Arg	Pro	Asp	Val	Thr	Gln	Pro	Val	Pro	Lys	65	70	75	80
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Met	Asn	Glu	Leu	Met	Glu	Gln	Thr	Ser	Glu	Ile	Ile	Thr	Phe	Ala	Glu	115	120	125	
Ser	Gly	Thr	Ala	Arg	Lys	Thr	Leu	His	Phe	Glu	Ile	Ser	Lys	Glu	Gly	130	135	140	
Ser	Asp	Leu	Ser	Val	Val	Glu	Arg	Ala	Glu	Val	Trp	Leu	Phe	Leu	Lys	145	150	155	160
Val	Pro	Lys	Ala	Asn	Arg	Thr	Arg	Thr	Lys	Val	Thr	Ile	Arg	Leu	Phe	165	170	175	
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Lys	Val	Val	Asp	Ala	Arg	Lys	Ser	Thr	Trp	His	Val	Phe	Pro	Val	Ser	210	215	220	
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Cys	Cys	Lys	Lys	Gln	Phe	Phe	Val	Ser	Phe	Lys	Asp	Ile	Gly	Trp	Asn	325	330	335	
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Glu	Cys	Pro	Ser	His	Ile	Ala	Gly	Thr	Ser	Gly	Ser	Ser	Leu	Ser	Phe	355	360	365	
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370	375	380
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385	390	395
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Asn Met Ile Val Glu Glu Cys Gly Cys Ser		415
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<210> 96
 <211> 4637
 <212> DNA
 <213> Homo sapiens

<400> 96

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<210> 97

<211> 1051

<212> PRT

<213> Homo sapiens

<400> 97

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<212> DNA

<213> Homo sapiens

<400> 98

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<400> 99

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<211> 408

<212> PRT

<213> Homo sapiens

<400> 105

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Thr	Trp	Val	Thr	Phe	Gly	Gly	Gln	Ile	Ser	Asp	Glu	Val	Ala	Glu	Arg			
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			355				360					365						
Glu	Gln	Leu	Ile	Glu	Asn	Leu	Gly	Ala	Ile	Gln	Val	Leu	Pro	Lys	Met			
			370			375				380								
Thr	Ser	His	Val	Val	Asn	Glu	Ile	Asp	Asn	Ile	Leu	Arg	Asn	Lys	Pro			
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<211> 3103

<212> DNA

<213> Homo sapiens

<400> 106

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<211> 419

<212> PRT

<213> Homo sapiens

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Pro Ser Gly Glu Ser Gln Leu Arg Ala Arg Gln Leu Ala Leu Leu Arg			
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Glu Val Glu Met Asn Trp Tyr Leu Lys Leu Cys Asp Leu Ser Ser Glu			
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His Thr Thr Val Cys Thr Thr Gly Met Pro His Arg Asn Leu Gly Lys			
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Gly Lys Ala Glu Val Ile Leu Gly Ser Ile Ile Lys Lys Lys Gly Trp			
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Arg Arg Ser Ser Leu Val Ile Thr Thr Lys Leu Tyr Trp Gly Gly Lys			
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Lys Gly Ser Leu Gln Arg Leu Gln Leu Glu Tyr Val Asp Val Val Phe			
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<400> 108

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<210> 115

<211> 1193

<212> PRT

<213> Homo sapiens

<400> 115

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Lys Ser Arg Gln Cys Ile Phe Asp Arg Glu Leu His Arg Gln Thr Gly
 35           40           45
Asn Gly Phe Arg Cys Leu Asn Cys Asn Asp Asn Thr Asp Gly Ile His
 50           55           60
Cys Glu Lys Cys Lys Asn Gly Phe Tyr Arg His Arg Glu Arg Asp Arg
 65           70           75           80
Cys Leu Pro Cys Asn Cys Asn Ser Lys Gly Ser Leu Ser Ala Arg Cys
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Asp	Asn	Ser	Gly	Arg	Cys	Ser	Cys	Lys	Pro	Gly	Val	Thr	Gly	Ala	Arg	
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Glu	His	Pro	Ser	Asn	Asn	Trp	Ser	Pro	Gln	Leu	Ser	Tyr	Phe	Glu	Tyr	
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Arg	Arg	Leu	Leu	Arg	Asn	Leu	Thr	Ala	Leu	Arg	Ile	Arg	Ala	Thr	Tyr	
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			740					745					750			
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 Glu Gly Glu Leu Glu Arg Lys Glu Leu Glu Phe Asp Thr Asn Met Asp
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 Ala Val Gln Met Val Ile Thr Glu Ala Gln Lys Val Asp Thr Arg Ala
 1075 1080 1085
 Lys Asn Ala Gly Val Thr Ile Gln Asp Thr Leu Asn Thr Leu Asp Gly
 1090 1095 1100
 Leu Leu His Leu Met Asp Gln Pro Leu Ser Val Asp Glu Glu Gly Leu
 1105 1110 1115 1120
 Val Leu Leu Glu Gln Lys Leu Ser Arg Ala Lys Thr Gln Ile Asn Ser
 1125 1130 1135
 Gln Leu Arg Pro Met Met Ser Glu Leu Glu Glu Arg Ala Arg Gln Gln
 1140 1145 1150
 Arg Gly His Leu His Leu Leu Glu Thr Ser Ile Asp Gly Ile Leu Ala
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 <212> DNA
 <213> Homo sapiens

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 aaaataaagg tgttttttggt taactgtcat tttgtttatt ctactgcagt agccagtgga 540
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 <211> 91
 <212> PRT
 <213> Homo sapiens

<400> 117
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 35 40 45
 Met Val Leu Glu Asp Val Thr Glu Phe Glu Ile Thr Pro Glu Gly Arg
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 Arg Ile Thr Lys Leu Asp Gln Ile Leu Leu Asn Gly Asn Asn Ile Thr
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85

90

<210> 118
 <211> 1717
 <212> DNA
 <213> Homo sapiens

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 cttaggaata accagattga ccatattgat gaaaaggcct ttgagaatgt aactgatctg 360
 cagtggctca ttctagatca caaccttcta gaaaactcca agataaaaagg gagagtcttc 420
 tctaaattga aacaactgaa gaagctgcac ataaaccaca acaacctgac agagtctgtg 480
 ggcccacttc ccaaattctc ggaggatctg cagcttactc ataacaagat cacaagctg 540
 ggctcttttg aaggattggg aaacctgacc ttcatccatc tccagcacia tcggctgaaa 600
 gaggatgctg ttctagctgc ttttaaaggc cttaaatcac tcgaatacct tgacttgagc 660
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 aacgaagtca ctcttaatta atatctgtat cctggaacaa tatcttatgg ttatgttttt 1140
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<210> 119
 <211> 338
 <212> PRT
 <213> Homo sapiens

<400> 119
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 35 40 45
 Ser Ala Met Tyr Cys Asp Glu Leu Lys Leu Lys Ser Val Pro Met Val
 50 55 60
 Pro Pro Gly Ile Lys Tyr Leu Tyr Leu Arg Asn Asn Gln Ile Asp His
 65 70 75 80
 Ile Asp Glu Lys Ala Phe Glu Asn Val Thr Asp Leu Gln Trp Leu Ile
 85 90 95
 Leu Asp His Asn Leu Leu Glu Asn Ser Lys Ile Lys Gly Arg Val Phe
 100 105 110

Ser Lys Leu Lys Gln Leu Lys Lys Leu His Ile Asn His Asn Asn Leu
 115 120 125
 Thr Glu Ser Val Gly Pro Leu Pro Lys Ser Leu Glu Asp Leu Gln Leu
 130 135 140
 Thr His Asn Lys Ile Thr Lys Leu Gly Ser Phe Glu Gly Leu Val Asn
 145 150 155 160
 Leu Thr Phe Ile His Leu Gln His Asn Arg Leu Lys Glu Asp Ala Val
 165 170 175
 Ser Ala Ala Phe Lys Gly Leu Lys Ser Leu Glu Tyr Leu Asp Leu Ser
 180 185 190
 Phe Asn Gln Ile Ala Arg Leu Pro Ser Gly Leu Pro Val Ser Leu Leu
 195 200 205
 Thr Leu Tyr Leu Asp Asn Asn Lys Ile Ser Asn Ile Pro Asp Glu Tyr
 210 215 220
 Phe Lys Arg Phe Asn Ala Leu Gln Tyr Leu Arg Leu Ser His Asn Glu
 225 230 235 240
 Leu Ala Asp Ser Gly Ile Pro Gly Asn Ser Phe Asn Val Ser Ser Leu
 245 250 255
 Val Glu Leu Asp Leu Ser Tyr Asn Lys Leu Lys Asn Ile Pro Thr Val
 260 265 270
 Asn Glu Asn Leu Glu Asn Tyr Tyr Leu Glu Val Asn Gln Leu Glu Lys
 275 280 285
 Phe Asp Ile Lys Ser Phe Cys Lys Ile Leu Gly Pro Leu Ser Tyr Ser
 290 295 300
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<210> 120
 <211> 1334
 <212> DNA
 <213> Homo sapiens

<400> 120
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actgtaacat ttgg 1334

<210> 121
<211> 195
<212> PRT
<213> Homo sapiens

<400> 121
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His Val Lys Ser Asn Gly Asp Leu Ser Pro Lys Gly Glu Gly Glu Ser
35 40 45
Pro Pro Val Asn Gly Thr Asp Glu Ala Ala Gly Ala Thr Gly Asp Ala
50 55 60
Ile Glu Pro Ala Pro Pro Ser Gln Gly Ala Glu Ala Lys Gly Glu Val
65 70 75 80
Pro Pro Lys Glu Thr Pro Lys Lys Lys Lys Lys Phe Ser Phe Lys Lys
85 90 95
Pro Phe Lys Leu Ser Gly Leu Ser Phe Lys Arg Asn Arg Lys Glu Gly
100 105 110
Gly Gly Asp Ser Ser Ala Ser Ser Pro Thr Glu Glu Glu Gln Glu Gln
115 120 125
Gly Glu Ile Gly Ala Cys Ser Asp Glu Gly Thr Ala Gln Glu Gly Lys
130 135 140
Ala Ala Ala Thr Pro Glu Ser Gln Glu Pro Gln Ala Lys Gly Ala Glu
145 150 155 160
Ala Ser Ala Ala Ser Glu Glu Glu Ala Gly Pro Gln Ala Thr Glu Pro
165 170 175
Ser Thr Pro Ser Gly Pro Glu Ser Gly Pro Thr Pro Ala Ser Ala Glu
180 185 190
Gln Asn Glu
195

<210> 122
<211> 1081
<212> DNA
<213> Homo sapiens

<400> 122
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gctgcctacc tcttcctgct attcctgcct gcaggcttgc tggctcaggg ccagtatgat 180
ctggacccgc tgccgccgtt ccctgaccac gtccagtaca ccactatag cgaccagatc 240
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cagttccagt cccagcagca agtccaacag gaagtcattc cagccccaac ccagaacca 360
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atggccagca gcggcctgtg ccaatccgtg gcggcctcct gtgccaggag ctgtgggagc 660
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 a 1081

<210> 123
 <211> 183
 <212> PRT
 <213> Homo sapiens

<400> 123
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 Val Gln Tyr Thr His Tyr Ser Asp Gln Ile Asp Asn Pro Asp Tyr Tyr
 35 40 45
 Asp Tyr Gln Glu Val Thr Pro Arg Pro Ser Glu Glu Gln Phe Gln Phe
 50 55 60
 Gln Ser Gln Gln Gln Val Gln Gln Glu Val Ile Pro Ala Pro Thr Pro
 65 70 75 80
 Glu Pro Gly Asn Ala Glu Leu Glu Pro Thr Glu Pro Gly Pro Leu Asp
 85 90 95
 Cys Arg Glu Glu Gln Tyr Pro Cys Thr Arg Leu Tyr Ser Ile His Arg
 100 105 110
 Pro Cys Lys Gln Cys Leu Asn Glu Val Cys Phe Tyr Ser Leu Arg Arg
 115 120 125
 Val Tyr Val Ile Asn Lys Glu Ile Cys Val Arg Thr Val Cys Ala His
 130 135 140
 Glu Glu Leu Leu Arg Ala Asp Leu Cys Arg Asp Lys Phe Ser Lys Cys
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 165 170 175
 Ala Arg Ser Cys Gly Ser Cys
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<210> 124
 <211> 1066
 <212> DNA
 <213> Homo sapiens

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1066

<210> 125
 <211> 183
 <212> PRT
 <213> Homo sapiens

<400> 125
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 35 40 45
 Asp Tyr Gln Glu Val Thr Pro Arg Pro Ser Glu Glu Gln Phe Gln Phe
 50 55 60
 Gln Ser Gln Gln Gln Val Gln Gln Glu Val Ile Pro Ala Pro Thr Pro
 65 70 75 80
 Glu Pro Gly Asn Ala Glu Leu Glu Pro Thr Glu Pro Gly Pro Leu Asp
 85 90 95
 Cys Arg Glu Glu Gln Tyr Pro Cys Thr Arg Leu Tyr Ser Ile His Arg
 100 105 110
 Pro Cys Lys Gln Cys Leu Asn Glu Val Cys Phe Tyr Ser Leu Arg Arg
 115 120 125
 Val Tyr Val Ile Asn Lys Glu Ile Cys Val Arg Thr Val Cys Ala His
 130 135 140
 Glu Glu Leu Leu Arg Ala Asp Leu Cys Arg Asp Lys Phe Ser Lys Cys
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 Gly Val Met Ala Ser Ser Gly Leu Cys Gln Ser Val Ala Ala Ser Cys
 165 170 175
 Ala Arg Ser Cys Gly Ser Cys
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<210> 126
 <211> 1611
 <212> DNA
 <213> Homo sapiens

<400> 126
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<210> 127
 <211> 360
 <212> PRT
 <213> Homo sapiens

<400> 127

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Glu	Gly	Ala	Tyr	Gly	Met	Val	Cys	Ser	Ala	Tyr	Asp	Asn	Val	Asn	Lys	35	40	45	
Val	Arg	Val	Ala	Ile	Lys	Lys	Ile	Ser	Pro	Phe	Glu	His	Gln	Thr	Tyr	50	55	60	
Cys	Gln	Arg	Thr	Leu	Arg	Glu	Ile	Lys	Ile	Leu	Leu	Arg	Phe	Arg	His	65	70	75	80
Glu	Asn	Ile	Ile	Gly	Ile	Asn	Asp	Ile	Ile	Arg	Ala	Pro	Thr	Ile	Glu	85	90	95	
Gln	Met	Lys	Asp	Val	Tyr	Ile	Val	Gln	Asp	Leu	Met	Glu	Thr	Asp	Leu	100	105	110	
Tyr	Lys	Leu	Leu	Lys	Thr	Gln	His	Leu	Ser	Asn	Asp	His	Ile	Cys	Tyr	115	120	125	
Phe	Leu	Tyr	Gln	Ile	Leu	Arg	Gly	Leu	Lys	Tyr	Ile	His	Ser	Ala	Asn	130	135	140	
Val	Leu	His	Arg	Asp	Leu	Lys	Pro	Ser	Asn	Leu	Leu	Leu	Asn	Thr	Thr	145	150	155	160
Cys	Asp	Leu	Lys	Ile	Cys	Asp	Phe	Gly	Leu	Ala	Arg	Val	Ala	Asp	Pro	165	170	175	
Asp	His	Asp	His	Thr	Gly	Phe	Leu	Thr	Glu	Tyr	Val	Ala	Thr	Arg	Trp	180	185	190	
Tyr	Arg	Ala	Pro	Glu	Ile	Met	Leu	Asn	Ser	Lys	Gly	Tyr	Thr	Lys	Ser	195	200	205	
Ile	Asp	Ile	Trp	Ser	Val	Gly	Cys	Ile	Leu	Ala	Glu	Met	Leu	Ser	Asn	210	215	220	
Arg	Pro	Ile	Phe	Pro	Gly	Lys	His	Tyr	Leu	Asp	Gln	Leu	Asn	His	Ile	225	230	235	240
Leu	Gly	Ile	Leu	Gly	Ser	Pro	Ser	Gln	Glu	Asp	Leu	Asn	Cys	Ile	Ile	245	250	255	
Asn	Leu	Lys	Ala	Arg	Asn	Tyr	Leu	Leu	Ser	Leu	Pro	His	Lys	Asn	Lys	260	265	270	
Val	Pro	Trp	Asn	Arg	Leu	Phe	Pro	Asn	Ala	Asp	Ser	Lys	Ala	Leu	Asp	275	280	285	
Leu	Leu	Asp	Lys	Met	Leu	Thr	Phe	Asn	Pro	His	Lys	Arg	Ile	Glu	Val	290	295	300	
Glu	Gln	Ala	Leu	Ala	His	Pro	Tyr	Leu	Glu	Gln	Tyr	Tyr	Asp	Pro	Ser	305	310	315	320
Asp	Glu	Pro	Ile	Ala	Glu	Ala	Pro	Phe	Lys	Phe	Asp	Met	Glu	Leu	Asp	325	330	335	
Asp	Leu	Pro	Lys	Glu	Lys	Leu	Lys	Glu	Leu	Ile	Phe	Glu	Glu	Thr	Ala	340	345	350	

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<210> 128
<211> 2917
<212> DNA
<213> Homo sapiens

<400> 128

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<210> 129
 <211> 821
 <212> PRT
 <213> Homo sapiens

<400> 129

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			20					25					30		
Phe	Leu	Glu	Glu	Phe	Gln	Ser	Ser	Asp	Gly	Glu	Ile	Lys	Tyr	Leu	Gln
		35					40					45			
Leu	Ala	Glu	Glu	Leu	Ile	Arg	Pro	Glu	Arg	Asn	Thr	Leu	Val	Val	Ser
	50					55					60				
Phe	Val	Asp	Leu	Glu	Gln	Phe	Asn	Gln	Gln	Leu	Ser	Thr	Thr	Ile	Gln
65					70					75					80
Glu	Glu	Phe	Tyr	Arg	Val	Tyr	Pro	Tyr	Leu	Cys	Arg	Ala	Leu	Lys	Thr
			85						90					95	
Phe	Val	Lys	Asp	Arg	Lys	Glu	Ile	Pro	Leu	Ala	Lys	Asp	Phe	Tyr	Val
			100					105					110		
Ala	Phe	Gln	Asp	Leu	Pro	Thr	Arg	His	Lys	Ile	Arg	Glu	Leu	Thr	Ser
		115					120					125			
Ser	Arg	Ile	Gly	Leu	Leu	Thr	Arg	Ile	Ser	Gly	Gln	Val	Val	Arg	Thr
	130					135					140				
His	Pro	Val	His	Pro	Glu	Leu	Val	Ser	Gly	Thr	Phe	Leu	Cys	Leu	Asp
145					150					155					160
Cys	Gln	Thr	Val	Ile	Arg	Asp	Val	Glu	Gln	Gln	Phe	Lys	Tyr	Thr	Gln
			165						170					175	
Pro	Asn	Ile	Cys	Arg	Asn	Pro	Val	Cys	Ala	Asn	Arg	Arg	Arg	Phe	Leu
			180					185					190		
Leu	Asp	Thr	Asn	Lys	Ser	Arg	Phe	Val	Asp	Phe	Gln	Lys	Val	Arg	Ile
	195						200					205			
Gln	Glu	Thr	Gln	Ala	Glu	Leu	Pro	Arg	Gly	Ser	Ile	Pro	Arg	Ser	Leu
	210					215					220				
Glu	Val	Ile	Leu	Arg	Ala	Glu	Ala	Val	Glu	Ser	Ala	Gln	Ala	Gly	Asp
225					230					235					240
Lys	Cys	Asp	Phe	Thr	Gly	Thr	Leu	Ile	Val	Val	Pro	Asp	Val	Ser	Lys
			245						250					255	
Leu	Ser	Thr	Pro	Gly	Ala	Arg	Ala	Glu	Thr	Asn	Ser	Arg	Val	Ser	Gly
			260					265					270		
Val	Asp	Gly	Tyr	Glu	Thr	Glu	Gly	Ile	Arg	Gly	Leu	Arg	Ala	Leu	Gly
	275						280					285			
Val	Arg	Asp	Leu	Ser	Tyr	Arg	Leu	Val	Phe	Leu	Ala	Cys	Cys	Val	Ala
	290					295					300				
Pro	Thr	Asn	Pro	Arg	Phe	Gly	Gly	Lys	Glu	Leu	Arg	Asp	Glu	Glu	Gln
305					310					315					320
Thr	Ala	Glu	Ser	Ile	Lys	Asn	Gln	Met	Thr	Val	Lys	Glu	Trp	Glu	Lys
			325						330					335	
Val	Phe	Glu	Met	Ser	Gln	Asp	Lys	Asn	Leu	Tyr	His	Asn	Leu	Cys	Thr
			340					345					350		
Ser	Leu	Phe	Pro	Thr	Ile	His	Gly	Asn	Asp	Glu	Val	Lys	Arg	Gly	Val
	355						360					365			
Leu	Leu	Met	Leu	Phe	Gly	Gly	Val	Pro	Lys	Thr	Thr	Gly	Glu	Gly	Thr
	370					375					380				
Ser	Leu	Arg	Gly	Asp	Ile	Asn	Val	Cys	Ile	Val	Gly	Asp	Pro	Ser	Thr
385					390					395					400
Ala	Lys	Ser	Gln	Phe	Leu	Lys	His	Val	Glu	Glu	Phe	Ser	Pro	Arg	Ala
			405						410					415	

Val	Tyr	Thr	Ser	Gly	Lys	Ala	Ser	Ser	Ala	Ala	Gly	Leu	Thr	Ala	Ala	
			420					425					430			
Val	Val	Arg	Asp	Glu	Glu	Ser	His	Glu	Phe	Val	Ile	Glu	Ala	Gly	Ala	
		435					440					445				
Leu	Met	Leu	Ala	Asp	Asn	Gly	Val	Cys	Cys	Ile	Asp	Glu	Phe	Asp	Lys	
	450					455					460					
Met	Asp	Val	Arg	Asp	Gln	Val	Ala	Ile	His	Glu	Ala	Met	Glu	Gln	Gln	
465					470					475					480	
Thr	Ile	Ser	Ile	Thr	Lys	Ala	Gly	Val	Lys	Ala	Thr	Leu	Asn	Ala	Arg	
			485						490					495		
Thr	Ser	Ile	Leu	Ala	Ala	Ala	Asn	Pro	Ile	Ser	Gly	His	Tyr	Asp	Arg	
			500					505					510			
Ser	Lys	Ser	Leu	Lys	Gln	Asn	Ile	Asn	Leu	Ser	Ala	Pro	Ile	Met	Ser	
		515					520					525				
Arg	Phe	Asp	Leu	Phe	Phe	Ile	Leu	Val	Asp	Glu	Cys	Asn	Glu	Val	Thr	
	530					535					540					
Asp	Tyr	Ala	Ile	Ala	Arg	Arg	Ile	Val	Asp	Leu	His	Ser	Arg	Ile	Glu	
545					550					555					560	
Glu	Ser	Ile	Asp	Arg	Val	Tyr	Ser	Leu	Asp	Asp	Ile	Arg	Arg	Tyr	Leu	
			565						570					575		
Leu	Phe	Ala	Arg	Gln	Phe	Lys	Pro	Lys	Ile	Ser	Lys	Glu	Ser	Glu	Asp	
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Phe	Ile	Val	Glu	Gln	Tyr	Lys	His	Leu	Arg	Gln	Arg	Asp	Gly	Ser	Gly	
		595					600					605				
Val	Thr	Lys	Ser	Ser	Trp	Arg	Ile	Thr	Val	Arg	Gln	Leu	Glu	Ser	Met	
	610					615					620					
Ile	Arg	Leu	Ser	Glu	Ala	Met	Ala	Arg	Met	His	Cys	Cys	Asp	Glu	Val	
625					630					635					640	
Gln	Pro	Lys	His	Val	Lys	Glu	Ala	Phe	Arg	Leu	Leu	Asn	Lys	Ser	Ile	
			645						650					655		
Ile	Arg	Val	Glu	Thr	Pro	Asp	Val	Asn	Leu	Asp	Gln	Glu	Glu	Glu	Ile	
			660					665					670			
Gln	Met	Glu	Val	Asp	Glu	Gly	Ala	Gly	Gly	Ile	Asn	Gly	His	Ala	Asp	
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Ser	Pro	Ala	Pro	Val	Asn	Gly	Ile	Asn	Gly	Tyr	Asn	Glu	Asp	Ile	Asn	
	690					695					700					
Gln	Glu	Ser	Ala	Pro	Lys	Ala	Ser	Leu	Arg	Leu	Gly	Phe	Ser	Glu	Tyr	
705					710					715					720	
Cys	Arg	Ile	Ser	Asn	Leu	Ile	Val	Leu	His	Leu	Arg	Lys	Val	Glu	Glu	
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Glu	Glu	Asp	Glu	Ser	Ala	Leu	Lys	Arg	Ser	Glu	Leu	Val	Asn	Trp	Tyr	
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Leu	Lys	Glu	Ile	Glu	Ser	Glu	Ile	Asp	Ser	Glu	Glu	Glu	Leu	Ile	Asn	
		755					760					765				
Lys	Lys	Arg	Ile	Ile	Glu	Lys	Val	Ile	His	Arg	Leu	Thr	His	Tyr	Asp	
	770					775					780					
His	Val	Leu	Ile	Glu	Leu	Thr	Gln	Ala	Gly	Leu	Lys	Gly	Ser	Thr	Glu	
785					790					795					800	
Gly	Ser	Glu	Ser	Tyr	Glu	Glu	Asp	Pro	Tyr	Leu	Val	Val	Asn	Pro	Asn	
			805						810					815		
Tyr	Leu	Leu	Glu	Asp												
			820													

<210> 130

<211> 786

<212> DNA

<213> Homo sapiens

<400> 130

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cccggggagc gagtgcgctg agtgggcctg ggggccctgc acccccagca gcaaggattg 180
cggcgtgggt ttccgcgagg gcacctgcgg ggcccagacc cagcgcaccc ggtgcagggt 240
gccctgcaac tggaagaagg agtttggagc cgactgcaag tacaagtttg agaactgggg 300
tgcgtgtgat gggggcacag gcaccaaagt ccgccaaggc accctgaaga aggcgcgcta 360
caatgctcag tgccaggaga ccatccgcgt caccaagccc tgcaccccca agaccaagc 420
aaaggccaaa gccaaagaaag ggaagggaaa ggactagacg ccaagcctgg atgccaagga 480
gcccctgggtg tcacatgggg cctggccacg ccctccctct cccaggcccg agatgtgacc 540
caccagtgcc ttctgtctgc tcgttagctt taatcaatca tgccctgcct tgtccctctc 600
actccccagc cccaccccta agtgcccaaa gtgggggaggg acaagggatt ctgggaagct 660
tgagcctccc ccaaagcaat gtgagtcca gagcccgctt ttgttcttcc ccacaattcc 720
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taatat                                           786

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<210> 131

<211> 143

<212> PRT

<213> Homo sapiens

<400> 131

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Met Gln His Arg Gly Phe Leu Leu Leu Thr Leu Leu Ala Leu Leu Ala
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Leu Thr Ser Ala Val Ala Lys Lys Lys Asp Lys Val Lys Lys Gly Gly
          20          25          30
Pro Gly Ser Glu Cys Ala Glu Trp Ala Trp Gly Pro Cys Thr Pro Ser
          35          40          45
Ser Lys Asp Cys Gly Val Gly Phe Arg Glu Gly Thr Cys Gly Ala Gln
          50          55          60
Thr Gln Arg Ile Arg Cys Arg Val Pro Cys Asn Trp Lys Lys Glu Phe
          65          70          75          80
Gly Ala Asp Cys Lys Tyr Lys Phe Glu Asn Trp Gly Ala Cys Asp Gly
          85          90          95
Gly Thr Gly Thr Lys Val Arg Gln Gly Thr Leu Lys Lys Ala Arg Tyr
          100          105          110
Asn Ala Gln Cys Gln Glu Thr Ile Arg Val Thr Lys Pro Cys Thr Pro
          115          120          125
Lys Thr Lys Ala Lys Ala Lys Ala Lys Lys Gly Lys Gly Lys Asp
          130          135          140

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<210> 132

<211> 603

<212> DNA

<213> Homo sapiens

<400> 132

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catggaatct tatgaactta atcccttcat taacaggaga aatgcaaata ccttcatatc 180
ccctcagcag agatggagag cttaaagtcca agagaggatc cgagaacgct ctaagcctgt 240
ccacgagctc aataggggaag cctgtgatga ctacagactt tgccaacgct acgcatggt 300
ttatggatac aatgctgcct ataatcgcta cttcaggaag cgccgagggg ccaaatgaga 360
ctgagggaag aaaaaaatc tctttttttc tggaggctgg cacctgattt tgtatcccc 420
tgtagcagca ttactgaaat acataggctt atatacaatg cttctttcct gtatatcttc 480
ttgtctggct gcacccttt ttcccgcccc cagattgata agtaatgaaa gtgcactgca 540
gtgagggtca aaggagagtc aacatatgtg attgttccat aataaacttc tgggtgtgata 600
ctt                                           603

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<210> 133
 <211> 103
 <212> PRT
 <213> Homo sapiens

<400> 133
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 Thr Leu Cys Tyr Glu Ser His Glu Ser Met Glu Ser Tyr Glu Leu Asn
 20 25 30
 Pro Phe Ile Asn Arg Arg Asn Ala Asn Thr Phe Ile Ser Pro Gln Gln
 35 40 45
 Arg Trp Arg Ala Lys Val Gln Glu Arg Ile Arg Glu Arg Ser Lys Pro
 50 55 60
 Val His Glu Leu Asn Arg Glu Ala Cys Asp Asp Tyr Arg Leu Cys Glu
 65 70 75 80
 Arg Tyr Ala Met Val Tyr Gly Tyr Asn Ala Ala Tyr Asn Arg Tyr Phe
 85 90 95
 Arg Lys Arg Arg Gly Ala Lys
 100

<210> 134
 <211> 1778
 <212> DNA
 <213> Homo sapiens

<400> 134
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 ttagaaaaat tttatggcct tgagataaac aaacttccag tgacaaaaat gaaatatagt 180
 ggaaacttaa tgaaggaaaa aatccaagaa atgcagcact tcttgggtct gaaagtgacc 240
 gggcaactgg acacatctac cctggagatg atgcacgcac ctcgatgtgg agtccccgat 300
 ctccatcatt tcagggaat gccagggggg cccgtatgga ggaaacatta tatcacctac 360
 agaatcaata attacacacc tgacatgaac cgtgaggatg ttgactacgc aatccggaaa 420
 gctttccaag tatggagtaa tgttaccccc ttgaaattca gcaagattaa cacaggcatg 480
 gctgacattt tgggtggttt tgcccgtgga gctcatggag acttccatgc ttttgatggc 540
 aaaggtggaa tcctagccca tgcttttgga cctggatctg gcattggagg ggatgcacat 600
 ttcgatgagg acgaattctg gactacacat tcaggaggca caaacttgtt cctcactgct 660
 gttcacgaga ttggccattc cttaggtctt ggccattcta gtgatccaaa ggctgtaatg 720
 ttccccacct acaaatatgt cgacatcaac acatttcgcc tctctgctga tgacatacgt 780
 ggcattcagt ccctgtatgg agacccaaaa gagaaccaac gcttgccaaa tcctgacaat 840
 tcagaaccag ctctctgtga cccaatttg agttttgatg ctgtcactac cgtgggaaat 900
 aagatctttt tcttcaaaga caggttcttc tggctgaagg tttctgagag accaaagacc 960
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 gaaattgaag ccagaaatca agtttttctt tttaaagatg acaaatactg gttaatttagc 1080
 aatttaagac cagagccaaa ttatcccaag agcatacatt cttttgggtt tcctaacttt 1140
 gtgaaaaaaa ttgatgcagc tgtttttaac ccacgttttt ataggacctt cttctttgta 1200
 gataaccagt attggaggta tgatgaaagg agacagatga tggaccctgg ttatcccaaa 1260
 ctgattacca agaacttcca aggaatcggg cctaaaattg atgcagtctt ctattctaaa 1320
 aacaaatact actatttctt ccaaggatct aaccaatttg aatatgactt cctactccaa 1380
 cgtatcacca aaacactgaa aagcaatagc tggtttggtt gttagaaatg gtgtaattaa 1440
 tgggtttttgt tagttcactt cagcttaata agtatattat gcataattgc tatgtcctca 1500
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 ttatatataaa tacataatat ttttcaattt tgaaaactct aattgtccat tcttgcttga 1620
 ctctactatt aagtttgaaa atagttacct tcaaagcaag ataattctat ttgaagcatg 1680
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 taaaattaag tatatatatt ttggctcaaa taaaattg 1778

<210> 135
 <211> 470
 <212> PRT
 <213> Homo sapiens

<400> 135
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 20 25 30
 Gly Glu Arg Tyr Leu Glu Lys Phe Tyr Gly Leu Glu Ile Asn Lys Leu
 35 40 45
 Pro Val Thr Lys Met Lys Tyr Ser Gly Asn Leu Met Lys Glu Lys Ile
 50 55 60
 Gln Glu Met Gln His Phe Leu Gly Leu Lys Val Thr Gly Gln Leu Asp
 65 70 75 80
 Thr Ser Thr Leu Glu Met Met His Ala Pro Arg Cys Gly Val Pro Asp
 85 90 95
 Leu His His Phe Arg Glu Met Pro Gly Gly Pro Val Trp Arg Lys His
 100 105 110
 Tyr Ile Thr Tyr Arg Ile Asn Asn Tyr Thr Pro Asp Met Asn Arg Glu
 115 120 125
 Asp Val Asp Tyr Ala Ile Arg Lys Ala Phe Gln Val Trp Ser Asn Val
 130 135 140
 Thr Pro Leu Lys Phe Ser Lys Ile Asn Thr Gly Met Ala Asp Ile Leu
 145 150 155 160
 Val Val Phe Ala Arg Gly Ala His Gly Asp Phe His Ala Phe Asp Gly
 165 170 175
 Lys Gly Gly Ile Leu Ala His Ala Phe Gly Pro Gly Ser Gly Ile Gly
 180 185 190
 Gly Asp Ala His Phe Asp Glu Asp Glu Phe Trp Thr Thr His Ser Gly
 195 200 205
 Gly Thr Asn Leu Phe Leu Thr Ala Val His Glu Ile Gly His Ser Leu
 210 215 220
 Gly Leu Gly His Ser Ser Asp Pro Lys Ala Val Met Phe Pro Thr Tyr
 225 230 235 240
 Lys Tyr Val Asp Ile Asn Thr Phe Arg Leu Ser Ala Asp Asp Ile Arg
 245 250 255
 Gly Ile Gln Ser Leu Tyr Gly Asp Pro Lys Glu Asn Gln Arg Leu Pro
 260 265 270
 Asn Pro Asp Asn Ser Glu Pro Ala Leu Cys Asp Pro Asn Leu Ser Phe
 275 280 285
 Asp Ala Val Thr Thr Val Gly Asn Lys Ile Phe Phe Phe Lys Asp Arg
 290 295 300
 Phe Phe Trp Leu Lys Val Ser Glu Arg Pro Lys Thr Ser Val Asn Leu
 305 310 315 320
 Ile Ser Ser Leu Trp Pro Thr Leu Pro Ser Gly Ile Glu Ala Ala Tyr
 325 330 335
 Glu Ile Glu Ala Arg Asn Gln Val Phe Leu Phe Lys Asp Asp Lys Tyr
 340 345 350
 Trp Leu Ile Ser Asn Leu Arg Pro Glu Pro Asn Tyr Pro Lys Ser Ile
 355 360 365
 His Ser Phe Gly Phe Pro Asn Phe Val Lys Lys Ile Asp Ala Ala Val
 370 375 380
 Phe Asn Pro Arg Phe Tyr Arg Thr Tyr Phe Phe Val Asp Asn Gln Tyr
 385 390 395 400
 Trp Arg Tyr Asp Glu Arg Arg Gln Met Met Asp Pro Gly Tyr Pro Lys
 405 410 415

Leu Ile Thr Lys Asn Phe Gln Gly Ile Gly Pro Lys Ile Asp Ala Val
 420 425 430
 Phe Tyr Ser Lys Asn Lys Tyr Tyr Tyr Phe Phe Gln Gly Ser Asn Gln
 435 440 445
 Phe Glu Tyr Asp Phe Leu Leu Gln Arg Ile Thr Lys Thr Leu Lys Ser
 450 455 460
 Asn Ser Trp Phe Gly Cys
 465 470

<210> 136
 <211> 1821
 <212> DNA
 <213> Homo sapiens

<400> 136
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 ttggatggag ctgcaagggg tgaggacacc agcatgaacc ttgttcagaa atatctagaa 180
 aactactacg acctcaaaaa agatgtgaaa cagtttggtta ggagaaagga cagtggtcct 240
 gttgttaaaa aaatccgaga aatgcagaag ttccttggat tggaggtgac ggggaagctg 300
 gactccgaca ctctggaggt gatgcgcaag ccaggtgtg gagttcctga tgttggtcac 360
 ttcagaacct ttcctggcat cccgaagtgg aggaaaaccc accttacata caggattgtg 420
 aattatacac cagatttgcc aaaagatgct gttgattctg ctgttgagaa agctctgaaa 480
 gtctgggaag aggtgactcc actcacattc tccaggctgt atgaaggaga ggctgatata 540
 atgatctctt ttgcagttag agaacatgga gacttttacc cttttgatgg acctggaaat 600
 gtttttggccc atgcctatgc ccctgggcca gggattaatg gagatgcca ctttgatgat 660
 gatgaacaat ggacaaagga tacaacaggg accaatttat ttctcgttgc tgctcatgaa 720
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 tatcactcac tcacagacct gactcgggtc cgctgtctc aagatgatat aaatggcatt 840
 cagtccctct atggacctcc ccctgactcc cctgagacc ccctgggtacc cacggaacct 900
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 gtggatgccg catatgaagt tactagcaag gacctcgttt tcatttttaa aggaaatcaa 1140
 ttctgggcca tcagaggaaa tgaggtacga gctggatacc caagaggcat ccacacccta 1200
 ggtttccctc caaccgtgag gaaaatcgat gcagccattt ctgataagga aaagaacaaa 1260
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 ccaggctttc ccaagcaaat agctgaagac tttccaggga ttgactcaaa gattgatgct 1380
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 ccaaatgcaa agaaagtgac acacactttg aagagtaaca gctggcttaa ttggtgaaag 1500
 agatatgtag aaggcacaat atgggcactt taaatgaagc taataattct tcacctaatg 1560
 ctctgtgaat tgaaatgttc gttttctcct gcctgtgctg tgactcgagt cacactcaag 1620
 ggaacttgag cgtgaatctg tatcttgccg gtcattttta tgttattaca gggcattcaa 1680
 atgggctgct gcttagcttg caccttgtca catagagtga tctttcccaa gagaagggga 1740
 agcactcgtg tgcaacagac aagtgactgt atctgtgtag actatttgct tatttaataa 1800
 agacgatttg tcagttgttt t 1821

<210> 137
 <211> 477
 <212> PRT
 <213> Homo sapiens

<400> 137
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 Ala Tyr Pro Leu Asp Gly Ala Ala Arg Gly Glu Asp Thr Ser Met Asn
 20 25 30
 Leu Val Gln Lys Tyr Leu Glu Asn Tyr Tyr Asp Leu Lys Lys Asp Val

		35				40			45								
Lys	Gln	Phe	Val	Arg	Arg	Lys	Asp	Ser	Gly	Pro	Val	Val	Lys	Lys	Ile		
	50					55					60						
Arg	Glu	Met	Gln	Lys	Phe	Leu	Gly	Leu	Glu	Val	Thr	Gly	Lys	Leu	Asp		
65					70					75					80		
Ser	Asp	Thr	Leu	Glu	Val	Met	Arg	Lys	Pro	Arg	Cys	Gly	Val	Pro	Asp		
				85					90					95			
Val	Gly	His	Phe	Arg	Thr	Phe	Pro	Gly	Ile	Pro	Lys	Trp	Arg	Lys	Thr		
			100					105					110				
His	Leu	Thr	Tyr	Arg	Ile	Val	Asn	Tyr	Thr	Pro	Asp	Leu	Pro	Lys	Asp		
		115					120					125					
Ala	Val	Asp	Ser	Ala	Val	Glu	Lys	Ala	Leu	Lys	Val	Trp	Glu	Glu	Val		
	130					135					140						
Thr	Pro	Leu	Thr	Phe	Ser	Arg	Leu	Tyr	Glu	Gly	Glu	Ala	Asp	Ile	Met		
145					150					155					160		
Ile	Ser	Phe	Ala	Val	Arg	Glu	His	Gly	Asp	Phe	Tyr	Pro	Phe	Asp	Gly		
				165					170					175			
Pro	Gly	Asn	Val	Leu	Ala	His	Ala	Tyr	Ala	Pro	Gly	Pro	Gly	Ile	Asn		
			180				185						190				
Gly	Asp	Ala	His	Phe	Asp	Asp	Asp	Glu	Gln	Trp	Thr	Lys	Asp	Thr	Thr		
	195					200						205					
Gly	Thr	Asn	Leu	Phe	Leu	Val	Ala	Ala	His	Glu	Ile	Gly	His	Ser	Leu		
	210					215					220						
Gly	Leu	Phe	His	Ser	Ala	Asn	Thr	Glu	Ala	Leu	Met	Tyr	Pro	Leu	Tyr		
225					230					235					240		
His	Ser	Leu	Thr	Asp	Leu	Thr	Arg	Phe	Arg	Leu	Ser	Gln	Asp	Asp	Ile		
				245					250					255			
Asn	Gly	Ile	Gln	Ser	Leu	Tyr	Gly	Pro	Pro	Pro	Asp	Ser	Pro	Glu	Thr		
			260				265						270				
Pro	Leu	Val	Pro	Thr	Glu	Pro	Val	Pro	Pro	Glu	Pro	Gly	Thr	Pro	Ala		
	275					280						285					
Asn	Cys	Asp	Pro	Ala	Leu	Ser	Phe	Asp	Ala	Val	Ser	Thr	Leu	Arg	Gly		
	290					295				300							
Glu	Ile	Leu	Ile	Phe	Lys	Asp	Arg	His	Phe	Trp	Arg	Lys	Ser	Leu	Arg		
305					310					315					320		
Lys	Leu	Glu	Pro	Glu	Leu	His	Leu	Ile	Ser	Ser	Phe	Trp	Pro	Ser	Leu		
				325					330					335			
Pro	Ser	Gly	Val	Asp	Ala	Ala	Tyr	Glu	Val	Thr	Ser	Lys	Asp	Leu	Val		
			340					345					350				
Phe	Ile	Phe	Lys	Gly	Asn	Gln	Phe	Trp	Ala	Ile	Arg	Gly	Asn	Glu	Val		
	355					360						365					
Arg	Ala	Gly	Tyr	Pro	Arg	Gly	Ile	His	Thr	Leu	Gly	Phe	Pro	Pro	Thr		
	370					375					380						
Val	Arg	Lys	Ile	Asp	Ala	Ala	Ile	Ser	Asp	Lys	Glu	Lys	Asn	Lys	Thr		
385					390					395					400		
Tyr	Phe	Phe	Val	Glu	Asp	Lys	Tyr	Trp	Arg	Phe	Asp	Glu	Lys	Arg	Asn		
				405					410					415			
Ser	Met	Glu	Pro	Gly	Phe	Pro	Lys	Gln	Ile	Ala	Glu	Asp	Phe	Pro	Gly		
			420				425						430				
Ile	Asp	Ser	Lys	Ile	Asp	Ala	Val	Phe	Glu	Glu	Phe	Gly	Phe	Phe	Tyr		
	435					440						445					
Phe	Phe	Thr	Gly	Ser	Ser	Gln	Leu	Glu	Phe	Asp	Pro	Asn	Ala	Lys	Lys		
	450					455					460						
Val	Thr	His	Thr	Leu	Lys	Ser	Asn	Ser	Trp	Leu	Asn	Cys					
465					470					475							

<210> 138

<211> 1127

<212> DNA

<213> Homo sapiens

<400> 138

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gaggcatgag tgagctacag tgggaacagg ctcaggacta tctcaagaga ttttatctct 180
atgactcaga aacaaaaaat gccaacagtt tagaagccaa actcaaggag atgcaaaaat 240
tctttggcct acctataact ggaatgttaa actcccgcgt catagaaata atgcagaagc 300
ccagatgtgg agtgccagat gttgcagaat actcactatt tccaaatagc ccaaaatgga 360
cttccaaagt ggtcacctac aggatcgtat catatactcg agacttaccg catattacag 420
tggatcgatt agtgtcaaag gcttttaaca tgtggggcaa agagatcccc ctgcatttca 480
ggaaagtgtg atggggaact gctgacatca tgattggctt tgcgcgagga gctcatgggg 540
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ggattaactt cctgtatgct gcaactcatg aacttggcca ttctttgggt atgggacatt 720
cctctgatcc taatgcagtg atgtatccaa cctatggaaa tggagatccc caaaatttta 780
aactttccca ggatgatatt aaaggcattc agaaactata tggaaagaga agtaattcaa 840
gaaagaaata gaaacttcag gcagaacatc cattcattca ttcattggat tgtatatcat 900
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cttttttatt gcagttgggt tttgaatgtc tttcactcct tttattgggt aaactccttt 1020
atggtgtgac tgtgtcttat tccatctatg agctttgtca gtgcgcgtag atgtcaataa 1080
atgttacata cacaaataaa taaaatgttt attccatggg aaattta 1127
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<210> 139

<211> 267

<212> PRT

<213> Homo sapiens

<400> 139

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          20          25          30
Glu Gln Ala Gln Asp Tyr Leu Lys Arg Phe Tyr Leu Tyr Asp Ser Glu
          35          40          45
Thr Lys Asn Ala Asn Ser Leu Glu Ala Lys Leu Lys Glu Met Gln Lys
          50          55          60
Phe Phe Gly Leu Pro Ile Thr Gly Met Leu Asn Ser Arg Val Ile Glu
          65          70          75          80
Ile Met Gln Lys Pro Arg Cys Gly Val Pro Asp Val Ala Glu Tyr Ser
          85          90          95
Leu Phe Pro Asn Ser Pro Lys Trp Thr Ser Lys Val Val Thr Tyr Arg
          100          105          110
Ile Val Ser Tyr Thr Arg Asp Leu Pro His Ile Thr Val Asp Arg Leu
          115          120          125
Val Ser Lys Ala Leu Asn Met Trp Gly Lys Glu Ile Pro Leu His Phe
          130          135          140
Arg Lys Val Val Trp Gly Thr Ala Asp Ile Met Ile Gly Phe Ala Arg
          145          150          155          160
Gly Ala His Gly Asp Ser Tyr Pro Phe Asp Gly Pro Gly Asn Thr Leu
          165          170          175
Ala His Ala Phe Ala Pro Gly Thr Gly Leu Gly Gly Asp Ala His Phe
          180          185          190
Asp Glu Asp Glu Arg Trp Thr Asp Gly Ser Ser Leu Gly Ile Asn Phe
          195          200          205
Leu Tyr Ala Ala Thr His Glu Leu Gly His Ser Leu Gly Met Gly His
          210          215          220
Ser Ser Asp Pro Asn Ala Val Met Tyr Pro Thr Tyr Gly Asn Gly Asp
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225		230		235		240									
Pro	Gln	Asn	Phe	Lys	Leu	Ser	Gln	Asp	Asp	Ile	Lys	Gly	Ile	Gln	Lys
				245					250					255	
Leu	Tyr	Gly	Lys	Arg	Ser	Asn	Ser	Arg	Lys	Lys					
			260					265							

<210> 140
 <211> 1078
 <212> DNA
 <213> Homo sapiens

<400> 140

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ctgcctggca	gcctggccct	gccgctgcct	caggaggcgg	gaggcatgag	tgagctacag	120
tgggaacagg	ctcaggacta	tctcaagaga	ttttatctct	atgactcaga	aacaaaaaat	180
gccaacagtt	tagaagccaa	actcaaggag	atgcaaaaat	tctttggcct	acctataact	240
ggaatgttaa	actcccgcgt	catagaaata	atgcagaagc	ccagatgtgg	agtgccagat	300
gttgcagaat	actcactatt	tccaaatagc	ccaaaatgga	cttccaaagt	ggtcacctac	360
aggatcgtat	catatactcg	agacttaccg	catattacag	tggatcgatt	agtgtcaaag	420
gcttttaaaca	tgtggggcaa	agagatcccc	ctgcatittca	ggaaagtgtg	atgggggaact	480
gctgacatca	tgattggctt	tgcgcgagga	gctcatgggg	actcctaccc	atgtgatggg	540
ccaggaaaca	cgctggctca	tgcctttgcg	cctgggacag	gtctcggagg	agatgctcac	600
ttcgatgagg	atgaacgctg	gacggatggg	agcagtctag	ggattaactt	cctgtatgct	660
gcaactcatg	aacttggcca	ttctttgggt	atgggacatt	cctctgatcc	taatgcagtg	720
atgtatccaa	cctatggaaa	tggagatccc	caaaatttta	aactttccca	ggatgatatt	780
aaaggcaftc	agaaactata	tggaaagaga	agtaattcaa	gaaagaaata	gaaacttcag	840
gcagaacatc	cattcattca	ttcattggat	tgtatatcat	tgttgacaaa	tcagaattga	900
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 <212> DNA
 <213> Homo sapiens

<400> 141

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<210> 142

<211> 707

<212> PRT

<213> Homo sapiens

<400> 142

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Gly Asp Leu Arg Thr Asn Leu Thr Asp Arg Gln Leu Ala Glu Glu Tyr
          35          40          45
Leu Tyr Arg Tyr Gly Tyr Thr Arg Val Ala Glu Met Arg Gly Glu Ser
          50          55          60
Lys Ser Leu Gly Pro Ala Leu Leu Leu Leu Gln Lys Gln Leu Ser Leu
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Pro Glu Thr Gly Glu Leu Asp Ser Ala Thr Leu Lys Ala Met Arg Thr
          85          90          95
Pro Arg Cys Gly Val Pro Asp Leu Gly Arg Phe Gln Thr Phe Glu Gly
          100          105          110
Asp Leu Lys Trp His His His Asn Ile Thr Tyr Trp Ile Gln Asn Tyr
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Ser Glu Asp Leu Pro Arg Ala Val Ile Asp Asp Ala Phe Ala Arg Ala
          130          135          140
Phe Ala Leu Trp Ser Ala Val Thr Pro Leu Thr Phe Thr Arg Val Tyr
          145          150          155          160
Ser Arg Asp Ala Asp Ile Val Ile Gln Phe Gly Val Ala Glu His Gly
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Asp Gly Tyr Pro Phe Asp Gly Lys Asp Gly Leu Leu Ala His Ala Phe
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Pro Pro Gly Pro Gly Ile Gln Gly Asp Ala His Phe Asp Asp Asp Glu
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Phe	Cys	Gln	Asp	Arg	Phe	Tyr	Trp	Arg	Val	Ser	Ser	Arg	Ser	Glu	Leu
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 <213> Homo sapiens

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<210> 144
 <211> 702
 <212> PRT
 <213> Homo sapiens

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 Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
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 Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
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Asp Asp Leu Asp Thr Leu Gly Leu Gly Leu Gln Gly Gly Ile Pro Asn						
		580		585		590
Gly Tyr Leu Val Leu Asp Leu Ser Val Gln Gly Gly Arg Gly Gly Gln						
		595		600		605
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		610		615		620
His Pro Ser Leu Cys Arg Gly Pro Leu Gly Asp Ala Leu Pro Pro Arg						
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Thr Trp Thr Cys Ser His Arg Pro Gly Thr Ala Pro Ser Leu His Pro						
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Gly Leu Arg Ala Pro Leu Pro Cys Trp Pro Gln Pro Cys Trp Gly Ser						
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Pro Pro Gly Gln Glu Gln Ala Arg Val Ile Pro Val Pro Pro Gln Glu						
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<210> 145

<211> 2135

<212> DNA

<213> Homo sapiens

<400> 145

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ctacggcagc ggcaggacga cctggacacg ctggggctgg ggctacaggg cggcatcccc 1860
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ctaggacctg gacctgttct caccgtcctg gcactgctcc tagcctccac cctggcctga 1980
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<210> 146

<211> 630

<212> PRT

<213> Homo sapiens

<400> 146

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			20					25					30		
Pro	Ser	Arg	Thr	Leu	Ala	Gly	Glu	Thr	Gly	Gln	Glu	Ala	Ala	Pro	Leu
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Asp	Gly	Val	Leu	Ala	Asn	Pro	Pro	Asn	Ile	Ser	Ser	Leu	Ser	Pro	Arg
	50				55					60					
Gln	Leu	Leu	Gly	Phe	Pro	Cys	Ala	Glu	Val	Ser	Gly	Leu	Ser	Thr	Glu
65					70					75					80
Arg	Val	Arg	Glu	Leu	Ala	Val	Ala	Leu	Ala	Gln	Lys	Asn	Val	Lys	Leu
				85					90					95	
Ser	Thr	Glu	Gln	Leu	Arg	Cys	Leu	Ala	His	Arg	Leu	Ser	Glu	Pro	Pro
			100					105					110		
Glu	Asp	Leu	Asp	Ala	Leu	Pro	Leu	Asp	Leu	Leu	Leu	Phe	Leu	Asn	Pro
		115					120					125			
Asp	Ala	Phe	Ser	Gly	Pro	Gln	Ala	Cys	Thr	Arg	Phe	Phe	Ser	Arg	Ile
	130					135					140				
Thr	Lys	Ala	Asn	Val	Asp	Leu	Leu	Pro	Arg	Gly	Ala	Pro	Glu	Arg	Gln
145					150					155					160
Arg	Leu	Leu	Pro	Ala	Ala	Leu	Ala	Cys	Trp	Gly	Val	Arg	Gly	Ser	Leu
				165					170					175	
Leu	Ser	Glu	Ala	Asp	Val	Arg	Ala	Leu	Gly	Gly	Leu	Ala	Cys	Asp	Leu
			180					185					190		
Pro	Gly	Arg	Phe	Val	Ala	Glu	Ser	Ala	Glu	Val	Leu	Leu	Pro	Arg	Leu
		195					200						205		
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Ser	Val	Ser	Thr	Met	Asp	Ala	Leu	Arg	Gly	Leu	Leu	Pro	Val	Leu	Gly
				245					250					255	
Gln	Pro	Ile	Ile	Arg	Ser	Ile	Pro	Gln	Gly	Ile	Val	Ala	Ala	Trp	Arg
			260					265					270		
Gln	Arg	Ser	Ser	Arg	Asp	Pro	Ser	Trp	Arg	Gln	Pro	Glu	Arg	Thr	Ile
		275					280					285			
Leu	Arg	Pro	Arg	Phe	Arg	Arg	Glu	Val	Glu	Lys	Thr	Ala	Cys	Pro	Ser
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Gly	Lys	Lys	Ala	Arg	Glu	Ile	Asp	Glu	Ser	Leu	Ile	Phe	Tyr	Lys	Lys
305					310					315					320
Trp	Glu	Leu	Glu	Ala	Cys	Val	Asp	Ala	Ala	Leu	Leu	Ala	Thr	Gln	Met
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Asp	Arg	Val	Asn	Ala	Ile	Pro	Phe	Thr	Tyr	Glu	Gln	Leu	Asp	Val	Leu
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Lys	His	Lys	Leu	Asp	Glu	Leu	Tyr	Pro	Gln	Gly	Tyr	Pro	Glu	Ser	Val
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Ile	Gln	His	Leu	Gly	Tyr	Leu	Phe	Leu	Lys	Met	Ser	Pro	Glu	Asp	Ile
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Arg	Lys	Trp	Asn	Val	Thr	Ser	Leu	Glu	Thr	Leu	Lys	Ala	Leu	Leu	Glu
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Val	Asn	Lys	Gly	His	Glu	Met	Ser	Pro	Gln	Ala	Pro	Arg	Arg	Pro	Leu
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Pro	Gln	Val	Ala	Thr	Leu	Ile	Asp	Arg	Phe	Val	Lys	Gly	Arg	Gly	Gln
			420					425					430		
Leu	Asp	Lys	Asp	Thr	Leu	Asp	Thr	Leu	Thr	Ala	Phe	Tyr	Pro	Gly	Tyr
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Leu	Cys	Ser	Leu	Ser	Pro	Glu	Glu	Leu	Ser	Ser	Val	Pro	Pro	Ser	Ser
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Ile	Trp	Ala	Val	Arg	Pro	Gln	Asp	Leu	Asp	Thr	Cys	Asp	Pro	Arg	Gln
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Leu	Asp	Val	Leu	Tyr	Pro	Lys	Ala	Arg	Leu	Ala	Phe	Gln	Asn	Met	Asn
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Gly	Ser	Glu	Tyr	Phe	Val	Lys	Ile	Gln	Ser	Phe	Leu	Gly	Gly	Ala	Pro
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Thr	Glu	Asp	Leu	Lys	Ala	Leu	Ser	Gln	Gln	Asn	Val	Ser	Met	Asp	Leu
		515					520					525			
Ala	Thr	Phe	Met	Lys	Leu	Arg	Thr	Asp	Ala	Val	Leu	Pro	Leu	Thr	Val
	530					535					540				
Ala	Glu	Val	Gln	Lys	Leu	Leu	Gly	Pro	His	Val	Glu	Gly	Leu	Lys	Ala
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Glu	Glu	Arg	His	Arg	Pro	Val	Arg	Asp	Trp	Ile	Leu	Arg	Gln	Arg	Gln
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Asp	Asp	Leu	Asp	Thr	Leu	Gly	Leu	Gly	Leu	Gln	Gly	Gly	Ile	Pro	Asn
			580					585					590		
Gly	Tyr	Leu	Val	Leu	Asp	Leu	Ser	Val	Gln	Glu	Ala	Leu	Ser	Gly	Thr
		595					600					605			
Pro	Cys	Leu	Leu	Gly	Pro	Gly	Pro	Val	Leu	Thr	Val	Leu	Ala	Leu	Leu
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Leu	Ala	Ser	Thr	Leu	Ala										
625					630										

<210> 147

<211> 2105

<212> DNA

<213> Homo sapiens

<400> 147

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tcctgtggga ccccgccct cggcagcctc ctgttcctgc tcttcagcct cggatgggtg 180
cagccctcga ggaccctggc tggagagaca gggcaggagg ctgcaccctt ggacggagtc 240
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gcggagggtg ccggcctgag cacggagcgt gtccgggagc tggctgtggc cttggcacag 360
aagaatgtca agctctcaac agagcagctg cgctgtcttg ctcaccggct ctctgagccc 420
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cggcaacgct cctctcgggg cccatccttg cggcagcctg aacggaccat cctccggccg 960
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gacgagagcc tcatcttcta caagaagtgg gagctggaag cctgcgtgga tgcggccctg 1080
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gctgggggatc cccgcctggc caggagcagg cacgggtgat ccccgttcca cccaagaga 2040
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<210> 148

<211> 620

<212> PRT

<213> Homo sapiens

<400> 148

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          20           25           30
Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
          35           40           45
Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
          50           55           60
Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
65           70           75           80
Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu
          85           90           95
Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
          100          105          110
Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro
          115          120          125
Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile
          130          135          140
Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln
145          150          155          160
Arg Leu Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu
          165          170          175
Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu
          180          185          190
Pro Gly Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu
          195          200          205
Val Ser Cys Pro Gly Pro Leu Asp Gln Asp Gln Gln Glu Ala Ala Arg
          210          215          220
Ala Ala Leu Gln Gly Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp
225          230          235          240
Ser Val Ser Thr Met Asp Ala Leu Arg Gly Leu Leu Pro Val Leu Gly
          245          250          255
Gln Pro Ile Ile Arg Ser Ile Pro Gln Gly Ile Val Ala Ala Trp Arg
          260          265          270
Gln Arg Ser Ser Arg Asp Pro Ser Trp Arg Gln Pro Glu Arg Thr Ile

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275	280	285
Leu Arg Pro Arg Phe Arg Arg Glu Val Glu Lys Thr Ala Cys Pro Ser		
290	295	300
Gly Lys Lys Ala Arg Glu Ile Asp Glu Ser Leu Ile Phe Tyr Lys Lys		
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Trp Glu Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Thr Gln Met		
325	330	335
Asp Arg Val Asn Ala Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu		
340	345	350
Lys His Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val		
355	360	365
Ile Gln His Leu Gly Tyr Leu Phe Leu Lys Met Ser Pro Glu Asp Ile		
370	375	380
Arg Lys Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu		
385	390	395
Val Asn Lys Gly His Glu Met Ser Pro Gln Ala Pro Arg Arg Pro Leu		
405	410	415
Pro Gln Val Ala Thr Leu Ile Asp Arg Phe Val Lys Gly Arg Gly Gln		
420	425	430
Leu Asp Lys Asp Thr Leu Asp Thr Leu Thr Ala Phe Tyr Pro Gly Tyr		
435	440	445
Leu Cys Ser Leu Ser Pro Glu Glu Leu Ser Ser Val Pro Pro Ser Ser		
450	455	460
Ile Trp Ala Val Arg Pro Gln Asp Leu Asp Thr Cys Asp Pro Arg Gln		
465	470	475
Leu Asp Val Leu Tyr Pro Lys Ala Arg Leu Ala Phe Gln Asn Met Asn		
485	490	495
Gly Ser Glu Tyr Phe Val Lys Ile Gln Ser Phe Leu Gly Gly Ala Pro		
500	505	510
Thr Glu Asp Leu Lys Ala Leu Ser Gln Gln Asn Val Ser Met Asp Leu		
515	520	525
Ala Thr Phe Met Lys Leu Arg Thr Asp Ala Val Leu Pro Leu Thr Val		
530	535	540
Ala Glu Val Gln Lys Leu Leu Gly Pro His Val Glu Gly Leu Lys Ala		
545	550	555
Glu Glu Arg His Arg Pro Val Arg Asp Trp Ile Leu Arg Gln Arg Gln		
565	570	575
Asp Asp Leu Asp Thr Leu Gly Leu Gly Leu Gln Gly Gly Ile Pro Asn		
580	585	590
Gly Tyr Leu Val Leu Asp Leu Ser Val Gln Gly Pro Gly Pro Val Leu		
595	600	605
Thr Val Leu Ala Leu Leu Leu Ala Ser Thr Leu Ala		
610	615	620

<210> 149

<211> 2193

<212> DNA

<213> Homo sapiens

<400> 149

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tcctgtggga cccccgccct cggcagcctc ctgttcctgc tcttcagcct cggatgggtg 180
cagccctcga ggaccctggc tggagagaca gggcaggagg ctgcaccctt ggacggagtc 240
ctggccaacc cacctaacat ttccagcctc tcccctcgcc aactccttgg cttcccgtgt 300
gcgagggtgt ccggcctgag cacggagcgt gtccgggagc tggctgtggc cttggcacag 360
aagaatgtca agctctcaac agagcagctg cgctgtctgg ctcaccggct ctctgagccc 420
cccgaggacc tggacgccct cccattggac ctgctgctat tcctcaaccc agatgcgttc 480

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<210> 150

<211> 694

<212> PRT

<213> Homo sapiens

<400> 150

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          20          25          30
Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
          35          40          45
Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
          50          55          60
Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
          65          70          75          80
Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu
          85          90          95
Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
          100          105          110
Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro
          115          120          125
Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile
          130          135          140
Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln
          145          150          155          160
Arg Leu Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu
          165          170          175
Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu

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			180					185					190			
Pro	Gly	Arg	Phe	Val	Ala	Glu	Ser	Ala	Glu	Val	Leu	Leu	Pro	Arg	Leu	
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Val	Ser	Cys	Pro	Gly	Pro	Leu	Asp	Gln	Asp	Gln	Gln	Glu	Ala	Ala	Arg	
	210					215					220					
Ala	Ala	Leu	Gln	Gly	Gly	Gly	Pro	Pro	Tyr	Gly	Pro	Pro	Ser	Thr	Trp	
225					230					235					240	
Ser	Val	Ser	Thr	Met	Asp	Ala	Leu	Arg	Gly	Leu	Leu	Pro	Val	Leu	Gly	
				245					250					255		
Gln	Pro	Ile	Ile	Arg	Ser	Ile	Pro	Gln	Gly	Ile	Val	Ala	Ala	Trp	Arg	
			260					265					270			
Gln	Arg	Ser	Ser	Arg	Asp	Pro	Ser	Trp	Arg	Gln	Pro	Glu	Arg	Thr	Ile	
		275					280					285				
Leu	Arg	Pro	Arg	Phe	Arg	Arg	Glu	Val	Glu	Lys	Thr	Ala	Cys	Pro	Ser	
	290					295					300					
Gly	Lys	Lys	Ala	Arg	Glu	Ile	Asp	Glu	Ser	Leu	Ile	Phe	Tyr	Lys	Lys	
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Trp	Glu	Leu	Glu	Ala	Cys	Val	Asp	Ala	Ala	Leu	Leu	Ala	Thr	Gln	Met	
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Asp	Arg	Val	Asn	Ala	Ile	Pro	Phe	Thr	Tyr	Glu	Gln	Leu	Asp	Val	Leu	
			340					345					350			
Lys	His	Lys	Leu	Asp	Glu	Leu	Tyr	Pro	Gln	Gly	Tyr	Pro	Glu	Ser	Val	
		355					360					365				
Ile	Gln	His	Leu	Gly	Tyr	Leu	Phe	Leu	Lys	Met	Ser	Pro	Glu	Asp	Ile	
	370					375					380					
Arg	Lys	Trp	Asn	Val	Thr	Ser	Leu	Glu	Thr	Leu	Lys	Ala	Leu	Leu	Glu	
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Arg	Phe	Val	Lys	Gly	Arg	Gly	Gln	Leu	Asp	Lys	Asp	Thr	Leu	Asp	Thr	
		420					425					430				
Leu	Thr	Ala	Phe	Tyr	Pro	Gly	Tyr	Leu	Cys	Ser	Leu	Ser	Pro	Glu	Glu	
	435					440					445					
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Arg	Leu	Ala	Phe	Gln	Asn	Met	Asn	Gly	Ser	Glu	Tyr	Phe	Val	Lys	Ile	
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		500						505					510			
Gln	Gln	Asn	Val	Ser	Met	Asp	Leu	Ala	Thr	Phe	Met	Lys	Leu	Arg	Thr	
		515					520					525				
Asp	Ala	Val	Leu	Pro	Leu	Thr	Val	Ala	Glu	Val	Gln	Lys	Leu	Leu	Gly	
	530					535					540					
Pro	His	Val	Glu	Gly	Leu	Lys	Ala	Glu	Glu	Arg	His	Arg	Pro	Val	Arg	
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Asp	Trp	Ile	Leu	Arg	Gln	Arg	Gln	Asp	Asp	Leu	Asp	Thr	Leu	Gly	Leu	
			565						570					575		
Gly	Leu	Gln	Gly	Gly	Ile	Pro	Asn	Gly	Tyr	Leu	Val	Leu	Asp	Leu	Ser	
		580						585					590			
Val	Gln	Gly	Gly	Arg	Gly	Gly	Gln	Ala	Arg	Ala	Gly	Gly	Arg	Ala	Gly	
	595						600					605				
Gly	Val	Glu	Val	Gly	Ala	Leu	Ser	His	Pro	Ser	Leu	Cys	Arg	Gly	Pro	
	610					615					620					
Leu	Gly	Asp	Ala	Leu	Pro	Pro	Arg	Thr	Trp	Thr	Cys	Ser	His	Arg	Pro	
625					630					635					640	
Gly	Thr	Ala	Pro	Ser	Leu	His	Pro	Gly	Leu	Arg	Ala	Pro	Leu	Pro	Cys	
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 <211> 2081
 <212> DNA
 <213> Homo sapiens

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<210> 152
 <211> 612
 <212> PRT
 <213> Homo sapiens

<400> 152
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Asp	Gly	Val	Leu	Ala	Asn	Pro	Pro	Asn	Ile	Ser	Ser	Leu	Ser	Pro	Arg	
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Gln	Leu	Leu	Gly	Phe	Pro	Cys	Ala	Glu	Val	Ser	Gly	Leu	Ser	Thr	Glu	
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				85					90					95		
Ser	Thr	Glu	Gln	Leu	Arg	Cys	Leu	Ala	His	Arg	Leu	Ser	Glu	Pro	Pro	
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Glu	Asp	Leu	Asp	Ala	Leu	Pro	Leu	Asp	Leu	Leu	Leu	Phe	Leu	Asn	Pro	
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Ser	Val	Ser	Thr	Met	Asp	Ala	Leu	Arg	Gly	Leu	Leu	Pro	Val	Leu	Gly	
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Gln	Pro	Ile	Ile	Arg	Ser	Ile	Pro	Gln	Gly	Ile	Val	Ala	Ala	Trp	Arg	
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Lys	His	Lys	Leu	Asp	Glu	Leu	Tyr	Pro	Gln	Gly	Tyr	Pro	Glu	Ser	Val	
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Ile	Gln	His	Leu	Gly	Tyr	Leu	Phe	Leu	Lys	Met	Ser	Pro	Glu	Asp	Ile	
					375						380					
Arg	Lys	Trp	Asn	Val	Thr	Ser	Leu	Glu	Thr	Leu	Lys	Ala	Leu	Leu	Glu	
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Leu	Thr	Ala	Phe	Tyr	Pro	Gly	Tyr	Leu	Cys	Ser	Leu	Ser	Pro	Glu	Glu	
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Leu	Ser	Ser	Val	Pro	Pro	Ser	Ser	Ile	Trp	Ala	Val	Arg	Pro	Gln	Asp	
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 530 535 540
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 545 550 555 560
 Asp Trp Ile Leu Arg Gln Arg Gln Asp Asp Leu Asp Thr Leu Gly Leu
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 580 585 590
 Val Gln Gly Pro Gly Pro Val Leu Thr Val Leu Ala Leu Leu Ala
 595 600 605
 Ser Thr Leu Ala
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 <211> 2111
 <212> DNA
 <213> Homo sapiens

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2111

<210> 154

<211> 622

<212> PRT

<213> Homo sapiens

<400> 154

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Pro	Ser	Arg	Thr	Leu	Ala	Gly	Glu	Thr	Gly	Gln	Glu	Ala	Ala	Pro	Leu
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Ser	Thr	Glu	Gln	Leu	Arg	Cys	Leu	Ala	His	Arg	Leu	Ser	Glu	Pro	Pro
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				165					170					175	
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			180					185					190		
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Val	Ser	Cys	Pro	Gly	Pro	Leu	Asp	Gln	Asp	Gln	Gln	Glu	Ala	Ala	Arg
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Ser	Val	Ser	Thr	Met	Asp	Ala	Leu	Arg	Gly	Leu	Leu	Pro	Val	Leu	Gly
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			260					265					270		
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Trp	Glu	Leu	Glu	Ala	Cys	Val	Asp	Ala	Ala	Leu	Leu	Ala	Thr	Gln	Met
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Lys	His	Lys	Leu	Asp	Glu	Leu	Tyr	Pro	Gln	Gly	Tyr	Pro	Glu	Ser	Val
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Pro	His	Val	Glu	Gly	Leu	Lys	Ala	Glu	Glu	Arg	His	Arg	Pro	Val	Arg		
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Asp	Trp	Ile	Leu	Arg	Gln	Arg	Gln	Asp	Asp	Leu	Asp	Thr	Leu	Gly	Leu		
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		580						585					590				
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<210> 155

<211> 1721

<212> DNA

<213> Homo sapiens

<400> 155

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<210> 156

<211> 515

<212> PRT

<213> Homo sapiens

<400> 156

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Thr Glu Lys Asn Ala Val Ser Met Thr Ser Ser Val Leu Ser Ser His
 50      55      60
Ser Pro Gly Ser Gly Ser Ser Thr Thr Gln Gly Gln Asp Val Thr Leu
 65      70      75      80
Ala Pro Ala Thr Glu Pro Ala Ser Gly Ser Ala Ala Thr Trp Gly Gln
 85      90      95
Asp Val Thr Ser Val Pro Val Thr Arg Pro Ala Leu Gly Ser Thr Thr
 100     105     110
Pro Pro Ala His Asp Val Thr Ser Ala Pro Asp Asn Lys Pro Ala Pro
 115     120     125
Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr
 130     135     140
Arg Pro Pro Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser
 145     150     155     160
Ala Pro Asp Thr Arg Pro Pro Pro Gly Ser Thr Ala Pro Ala Ala His
 165     170     175
Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala
 180     185     190
Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Asn Arg Pro Ala Leu
 195     200     205
Ala Ser Thr Ala Pro Pro Val His Asn Val Thr Ser Ala Ser Gly Ser
 210     215     220
Ala Ser Gly Ser Ala Ser Thr Leu Val His Asn Gly Thr Ser Ala Arg
 225     230     235     240
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His His Ser Asp Thr Pro Thr Thr Leu Ala Ser His Ser Thr Lys Thr
 260     265     270
Asp Ala Ser Ser Thr His His Ser Thr Val Pro Pro Leu Thr Ser Ser
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Asn His Ser Thr Ser Pro Gln Leu Ser Thr Gly Val Ser Phe Phe Phe
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Leu Ser Phe His Ile Ser Asn Leu Gln Phe Asn Ser Ser Leu Glu Asp
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Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp Ile Ser Glu Met
 325     330     335
Phe Leu Gln Ile Tyr Lys Gln Gly Gly Phe Leu Gly Leu Ser Asn Ile
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Lys Phe Arg Pro Gly Ser Val Val Val Gln Leu Thr Leu Ala Phe Arg
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Glu Gly Thr Ile Asn Val His Asp Val Glu Thr Gln Phe Asn Gln Tyr

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Pro Gly Trp Gly Ile Ala Leu Leu Val Leu Val Cys Val Leu Val Ala				
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Leu Ala Ile Val Tyr Leu Ile Ala Leu Ala Val Cys Gln Cys Arg Arg				
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Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala Arg Asp Thr Tyr His				
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Pro Met Ser Glu Tyr Pro Thr Tyr His Thr His Gly Arg Tyr Val Pro				
465		470		480
Pro Ser Ser Thr Asp Arg Ser Pro Tyr Glu Lys Val Ser Ala Gly Asn				
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<400> 157

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<211> 700

<212> PRT

<213> Homo sapiens

<400> 160

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<212> DNA

<213> Homo sapiens

<400> 161

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 <213> Homo sapiens

<400> 162

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<210> 164

<211> 1938

<212> PRT

<213> Homo sapiens

<400> 164

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Lys Arg Leu Val Trp Val Pro Ser Glu Lys Gln Gly Phe Glu Ala Ala
          35          40          45
Ser Ile Lys Glu Glu Lys Gly Asp Glu Val Val Val Glu Leu Val Glu
          50          55          60
Asn Gly Lys Lys Val Thr Val Gly Lys Asp Asp Ile Gln Lys Met Asn
          65          70          75          80
Pro Pro Lys Phe Ser Lys Val Glu Asp Met Ala Glu Leu Thr Cys Leu
          85          90          95
Asn Glu Ala Ser Val Leu His Asn Leu Arg Glu Arg Tyr Phe Ser Gly
          100          105          110
Leu Ile Tyr Thr Tyr Ser Gly Leu Phe Cys Val Val Val Asn Pro Tyr
          115          120          125
Lys His Leu Pro Ile Tyr Ser Glu Lys Ile Val Asp Met Tyr Lys Gly
          130          135          140
Lys Lys Arg His Glu Met Pro Pro His Ile Tyr Ala Ile Ala Asp Thr
          145          150          155          160
Ala Tyr Arg Ser Met Leu Gln Asp Arg Glu Asp Gln Ser Ile Leu Cys
          165          170          175
Thr Gly Glu Ser Gly Ala Gly Lys Thr Glu Asn Thr Lys Lys Val Ile
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Gln Tyr Leu Ala Val Val Ala Ser Ser His Lys Gly Lys Lys Asp Thr
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Ser Ile Thr Gly Glu Leu Glu Lys Gln Leu Leu Gln Ala Asn Pro Ile

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235

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	245	250
Val Gly Ala Asn Ile Glu Thr Tyr Leu Leu Glu Lys Ser Arg Ala Ile		255
	260	265
Arg Gln Ala Arg Asp Glu Arg Thr Phe His Ile Phe Tyr Tyr Met Ile		270
	275	280
Ala Gly Ala Lys Glu Lys Met Arg Ser Asp Leu Leu Leu Glu Gly Phe		285
	290	295
Asn Asn Tyr Thr Phe Leu Ser Asn Gly Phe Val Pro Ile Pro Ala Ala		300
305	310	315
Gln Asp Asp Glu Met Phe Gln Glu Thr Val Glu Ala Met Ala Ile Met		320
	325	330
Gly Phe Ser Glu Glu Glu Gln Leu Ser Ile Leu Lys Val Val Ser Ser		335
	340	345
Val Leu Gln Leu Gly Asn Ile Val Phe Lys Lys Glu Arg Asn Thr Asp		350
	355	360
Gln Ala Ser Met Pro Asp Asn Thr Ala Ala Gln Lys Val Cys His Leu		365
	370	375
Met Gly Ile Asn Val Thr Asp Phe Thr Arg Ser Ile Leu Thr Pro Arg		380
385	390	395
Ile Lys Val Gly Arg Asp Val Val Gln Lys Ala Gln Thr Lys Glu Gln		400
	405	410
Ala Asp Phe Ala Val Glu Ala Leu Ala Lys Ala Thr Tyr Glu Arg Leu		415
	420	425
Phe Arg Trp Ile Leu Thr Arg Val Asn Lys Ala Leu Asp Lys Thr His		430
	435	440
Arg Gln Gly Ala Ser Phe Leu Gly Ile Leu Asp Ile Ala Gly Phe Glu		445
	450	455
Ile Phe Glu Val Asn Ser Phe Glu Gln Leu Cys Ile Asn Tyr Thr Asn		460
465	470	475
Glu Lys Leu Gln Gln Leu Phe Asn His Thr Met Phe Ile Leu Glu Gln		480
	485	490
Glu Glu Tyr Gln Arg Glu Gly Ile Glu Trp Asn Phe Ile Asp Phe Gly		495
	500	505
Leu Asp Leu Gln Pro Cys Ile Glu Leu Ile Glu Arg Pro Asn Asn Pro		510
	515	520
Pro Gly Val Leu Ala Leu Leu Asp Glu Glu Cys Trp Phe Pro Lys Ala		525
	530	535
Thr Asp Lys Ser Phe Val Glu Lys Leu Cys Thr Glu Gln Gly Ser His		540
545	550	555
Pro Lys Phe Gln Lys Pro Lys Gln Leu Lys Asp Lys Thr Glu Phe Ser		560
	565	570
Ile Ile His Tyr Ala Gly Lys Val Asp Tyr Asn Ala Ser Ala Trp Leu		575
	580	585
Thr Lys Asn Met Asp Pro Leu Asn Asp Asn Val Thr Ser Leu Leu Asn		590
	595	600
Ala Ser Ser Asp Lys Phe Val Ala Asp Leu Trp Lys Asp Val Asp Arg		605
	610	615
Ile Val Gly Leu Asp Gln Met Ala Lys Met Thr Glu Ser Ser Leu Pro		620
625	630	635
Ser Ala Ser Lys Thr Lys Lys Gly Met Phe Arg Thr Val Gly Gln Leu		640
	645	650
Tyr Lys Glu Gln Leu Gly Lys Leu Met Thr Thr Leu Arg Asn Thr Thr		655
	660	665
Pro Asn Phe Val Arg Cys Ile Ile Pro Asn His Glu Lys Arg Ser Gly		670
	675	680
		685

Lys	Leu	Asp	Ala	Phe	Leu	Val	Leu	Glu	Gln	Leu	Arg	Cys	Asn	Gly	Val
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Leu	Glu	Gly	Ile	Arg	Ile	Cys	Arg	Gln	Gly	Phe	Pro	Asn	Arg	Ile	Val
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Phe	Gln	Glu	Phe	Arg	Gln	Arg	Tyr	Glu	Ile	Leu	Ala	Ala	Asn	Ala	Ile
				725					730					735	
Pro	Lys	Gly	Phe	Met	Asp	Gly	Lys	Gln	Ala	Cys	Ile	Leu	Met	Ile	Lys
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Ala	Leu	Glu	Leu	Asp	Pro	Asn	Leu	Tyr	Arg	Ile	Gly	Gln	Ser	Lys	Ile
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Phe	Phe	Arg	Thr	Gly	Val	Leu	Ala	His	Leu	Glu	Glu	Glu	Arg	Asp	Leu
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Lys	Ile	Thr	Asp	Val	Ile	Met	Ala	Phe	Gln	Ala	Met	Cys	Arg	Gly	Tyr
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Gln	Trp	Trp	Arg	Leu	Phe	Thr	Lys	Val	Lys	Pro	Leu	Leu	Gln	Val	Thr
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Lys	Glu	Arg	Gln	Gln	Lys	Ala	Glu	Asn	Glu	Leu	Lys	Glu	Leu	Glu	Gln
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Lys	His	Ser	Gln	Leu	Thr	Glu	Glu	Lys	Asn	Leu	Leu	Gln	Glu	Gln	Leu
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Gln	Ala	Glu	Thr	Glu	Leu	Tyr	Ala	Glu	Ala	Glu	Glu	Met	Arg	Val	Arg
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Leu	Ala	Ala	Lys	Lys	Gln	Glu	Leu	Glu	Glu	Ile	Leu	His	Glu	Met	Glu
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Ala	Arg	Leu	Glu	Glu	Glu	Glu	Asp	Arg	Gly	Gln	Gln	Leu	Gln	Ala	Glu
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Arg	Lys	Lys	Met	Ala	Gln	Gln	Met	Leu	Asp	Leu	Glu	Glu	Gln	Leu	Glu
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Glu	Glu	Glu	Ala	Ala	Arg	Gln	Lys	Leu	Gln	Leu	Glu	Lys	Val	Thr	Ala
			965						970					975	
Glu	Ala	Lys	Ile	Lys	Lys	Leu	Glu	Asp	Glu	Ile	Leu	Val	Met	Asp	Asp
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Gln	Asn	Asn	Lys	Leu	Ser	Lys	Glu	Arg	Lys	Leu	Leu	Glu	Glu	Arg	Ile
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Ser	Asp	Leu	Thr	Thr	Asn	Leu	Ala	Glu	Glu	Glu	Glu	Lys	Ala	Lys	Asn
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Leu	Thr	Lys	Leu	Lys	Asn	Lys	His	Glu	Ser	Met	Ile	Ser	Glu	Leu	Glu
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Val	Arg	Leu	Lys	Lys	Glu	Glu	Lys	Ser	Arg	Gln	Glu	Leu	Glu	Lys	Leu
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Lys	Arg	Lys	Leu	Glu	Gly	Asp	Ala	Ser	Asp	Phe	His	Glu	Gln	Ile	Ala
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	1090					1095					1100				
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Ser	Asp	Leu	Gln	Glu	Asp	Leu	Asp	Ser	Glu	Arg	Ala	Ala	Arg	Asn	Lys
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Ala	Glu	Lys	Gln	Lys	Arg	Asp	Leu	Gly	Glu	Glu	Leu	Glu	Ala	Leu	Lys
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Glu Val Glu His Lys Lys Lys Lys Leu Glu Ala Gln Val Gln Glu Leu		
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Lys Val His Lys Leu Gln Asn Glu Val Glu Ser Val Thr Gly Met Leu		
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Leu Ser Ser Gln Leu Gln Asp Thr Gln Glu Leu Leu Gln Glu Glu Thr		
1315	1320	1325
Arg Gln Lys Leu Asn Val Ser Thr Lys Leu Arg Gln Leu Glu Glu Glu		
1330	1335	1340
Arg Asn Ser Leu Gln Asp Gln Leu Asp Glu Glu Met Glu Ala Lys Gln		
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Asn Leu Glu Arg His Ile Ser Thr Leu Asn Ile Gln Leu Ser Asp Ser		
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1380	1385	1390
Gly Lys Lys Arg Phe Gln Lys Glu Ile Glu Asn Leu Thr Gln Gln Tyr		
1395	1400	1405
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Leu Gln Gln Glu Leu Asp Asp Leu Val Val Asp Leu Asp Asn Gln Arg		
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Gln Leu Val Ser Asn Leu Glu Lys Lys Gln Arg Lys Phe Asp Gln Leu		
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Leu Ala Glu Glu Lys Asn Ile Ser Ser Lys Tyr Ala Asp Glu Arg Asp		
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Ala Arg Ala Leu Glu Glu Ala Leu Glu Ala Lys Glu Glu Leu Glu Arg		
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Thr Asn Lys Met Leu Lys Ala Glu Met Glu Asp Leu Val Ser Ser Lys		
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Asp Asp Val Gly Lys Asn Val His Glu Leu Glu Lys Ser Lys Arg Ala		
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Leu Glu Thr Gln Met Glu Glu Met Lys Thr Gln Leu Glu Glu Leu Glu		
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Asp Glu Leu Gln Ala Thr Glu Asp Ala Lys Leu Arg Leu Glu Val Asn		
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Met Gln Ala Leu Lys Gly Gln Phe Glu Arg Asp Leu Gln Ala Arg Asp		
1570	1575	1580
Glu Gln Asn Glu Glu Lys Arg Arg Gln Leu Gln Arg Gln Leu His Glu		
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Tyr Glu Thr Glu Leu Glu Asp Glu Arg Lys Gln Arg Ala Leu Ala Ala		
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Ala Ala Lys Lys Lys Leu Glu Gly Asp Leu Lys Asp Leu Glu Leu Gln		
1620	1625	1630

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 1685 1690 1695
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 Leu Glu Glu Glu Gln Gly Asn Met Glu Ala Met Ser Asp Arg Val Arg
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 1765 1770 1775
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 1780 1785 1790
 Gln Asn Lys Glu Leu Arg Ser Lys Leu His Glu Met Glu Gly Ala Val
 1795 1800 1805
 Lys Ser Lys Phe Lys Ser Thr Ile Ala Ala Leu Glu Ala Lys Ile Ala
 1810 1815 1820
 Gln Leu Glu Glu Gln Val Glu Gln Glu Ala Arg Glu Lys Gln Ala Ala
 1825 1830 1835 1840
 Thr Lys Ser Leu Lys Gln Lys Asp Lys Lys Leu Lys Glu Ile Leu Leu
 1845 1850 1855
 Gln Val Glu Asp Glu Arg Lys Met Ala Glu Gln Tyr Lys Glu Gln Ala
 1860 1865 1870
 Glu Lys Gly Asn Ala Arg Val Lys Gln Leu Lys Arg Gln Leu Glu Glu
 1875 1880 1885
 Ala Glu Glu Glu Ser Gln Arg Ile Asn Ala Asn Arg Arg Lys Leu Gln
 1890 1895 1900
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 1925 1930 1935
 Ser Gln

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 <212> DNA
 <213> Homo sapiens

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 <212> PRT
 <213> Homo sapiens

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 35 40 45
 Arg Asp Lys Asp Pro Ala Leu Trp Cys Gln Leu Cys Leu Ser Ser Gln
 50 55 60
 His Gln Ala Ile Glu Arg Phe Tyr Asp Lys Met Gln Asn Ala Glu Ser
 65 70 75 80
 Gly Arg Gly Gln Val Met Ser Ser Leu Ala Glu Leu Glu Asp Asp Phe
 85 90 95
 Lys Glu Gly Tyr Leu Glu Thr Val Ala Ala Tyr Tyr Glu Glu Gln His
 100 105 110
 Pro Glu Leu Thr Pro Leu Leu Glu Lys Glu Arg Asp Gly Leu Arg Cys
 115 120 125
 Arg Gly Asn Arg Ser Pro Val Pro Asp Val Glu Asp Pro Ala Thr Glu
 130 135 140
 Glu Pro Gly Glu Ser Phe Cys Asx Lys Val Met Arg Trp Phe Gln Ala
 145 150 155 160
 Met Leu Gln Arg Leu Gln Thr Trp Trp His Gly Val Leu Ala Trp Val
 165 170 175
 Lys Glu Lys Val Val Ala Leu Val His Ala Val Gln Ala Leu Trp Lys
 180 185 190
 Gln Phe Gln Ser Phe Cys Cys Ser Leu Ser Glu Leu Phe Met Ser Ser
 195 200 205
 Phe Gln Ser Tyr Gly Ala Pro Arg Gly Asp Lys Glu Glu Leu Thr Pro
 210 215 220
 Gln Lys Cys Ser Glu Pro Gln Ser Ser Lys
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<211> 234

<212> PRT

<213> Homo sapiens

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Val Ser Ala Cys Asp Thr Glu Asp Thr Val Gly His Leu Gly Pro Trp
          35          40          45
Arg Asp Lys Asp Pro Ala Leu Trp Cys Gln Leu Cys Leu Ser Ser Gln
          50          55          60
His Gln Ala Ile Glu Arg Phe Tyr Asp Lys Met Gln Asn Ala Glu Ser
65          70          75          80
Gly Arg Gly Gln Val Met Ser Ser Leu Ala Glu Leu Glu Asp Asp Phe
          85          90          95
Lys Glu Gly Tyr Leu Glu Thr Val Ala Ala Tyr Tyr Glu Glu Gln His
          100          105          110
Pro Glu Leu Thr Pro Leu Leu Glu Lys Glu Arg Asp Gly Leu Arg Cys
          115          120          125
Arg Gly Asn Arg Ser Pro Val Pro Asp Val Glu Asp Pro Ala Thr Glu
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Glu Pro Gly Glu Ser Phe Cys Asp Lys Val Met Arg Trp Phe Gln Ala
145          150          155          160
Met Leu Gln Arg Leu Gln Thr Trp Trp His Gly Val Leu Ala Trp Val
          165          170          175
Lys Glu Lys Val Val Ala Leu Val His Ala Val Gln Ala Leu Trp Lys
          180          185          190
Gln Phe Gln Ser Phe Cys Cys Ser Leu Ser Glu Leu Phe Met Ser Ser
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Phe Gln Ser Tyr Gly Ala Pro Arg Gly Asp Lys Glu Glu Leu Thr Pro
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Gln Lys Cys Ser Glu Pro Gln Ser Ser Lys
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<210> 169

<211> 1005

<212> DNA

<213> Homo sapiens

<400> 169

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tgtgctgcta ttgtgtggat gccgcgcgtg tcttctcttc tttccagaga tggctaacag 60
gggcccagagc tatggcttaa gccgagaggt gcaggagaag atcgagcaga agtatgatgc 120
ggacctggag aacaagctgg tggactggat catcctgcag tgcgccgagg acatagagca 180
cccgccccc ggcagggccc attttcagaa atggttaatg gacgggacgg tcctgtgcaa 240
gctgataaat agtttatacc caccaggaca agagcccata cccaagatct cagagtcaaa 300
gatggctttt aagcagatgg agcaaatttc ccagttccta aaagctgcgg agacctatgg 360
tgtcagaacc accgacatct ttcagacggt ggatctatgg gaagggaagg acatggcagc 420

```

```

tgtgcagagg accctgatgg ctttaggcag cgttgcagtc accaaggatg atggctgcta 480
tcggggagag ccatcctggg ttacacaggaa agcccagcag aatcggagag gcttttccga 540
ggagcagctt cgccagggac agaacgtaat aggcctgcag atgggcagca acaagggagc 600
ctcccaggcg ggcatgacag ggtacgggat gcccaggcag atcatgttag gacgcggcat 660
cctgcccctg gtagagagga cgaatgttcc acaccatggg ctctacgaaa aagaaatagt 720
tagtcacctt ctgaccttct cctcttttctc aaagccttct gtccctgggtt tttgcaagtg 780
ctgcatttcc gccgagaatc cgcgttgccct actgctgccca cctcctgttc atttagaact 840
atgcaaagac tccgcttccg ttttcctgag ctccctcgggc cccagagtct ctgtttgatt 900
atttatttat ttatttat ttatttat atttgccaaa aattctcctc ttcaacttat agaatgcacc 960
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<210> 170

<211> 282

<212> PRT

<213> Homo sapiens

<400> 170

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Met Ala Asn Arg Gly Pro Ser Tyr Gly Leu Ser Arg Glu Val Gln Glu
 1          5          10          15
Lys Ile Glu Gln Lys Tyr Asp Ala Asp Leu Glu Asn Lys Leu Val Asp
          20          25          30
Trp Ile Ile Leu Gln Cys Ala Glu Asp Ile Glu His Pro Pro Pro Gly
          35          40          45
Arg Ala His Phe Gln Lys Trp Leu Met Asp Gly Thr Val Leu Cys Lys
          50          55          60
Leu Ile Asn Ser Leu Tyr Pro Pro Gly Gln Glu Pro Ile Pro Lys Ile
          65          70          75          80
Ser Glu Ser Lys Met Ala Phe Lys Gln Met Glu Gln Ile Ser Gln Phe
          85          90          95
Leu Lys Ala Ala Glu Thr Tyr Gly Val Arg Thr Thr Asp Ile Phe Gln
          100          105          110
Thr Val Asp Leu Trp Glu Gly Lys Asp Met Ala Ala Val Gln Arg Thr
          115          120          125
Leu Met Ala Leu Gly Ser Val Ala Val Thr Lys Asp Asp Gly Cys Tyr
          130          135          140
Arg Gly Glu Pro Ser Trp Phe His Arg Lys Ala Gln Gln Asn Arg Arg
          145          150          155          160
Gly Phe Ser Glu Glu Gln Leu Arg Gln Gly Gln Asn Val Ile Gly Leu
          165          170          175
Gln Met Gly Ser Asn Lys Gly Ala Ser Gln Ala Gly Met Thr Gly Tyr
          180          185          190
Gly Met Pro Arg Gln Ile Met Leu Gly Arg Gly Ile Leu Pro Leu Val
          195          200          205
Glu Arg Thr Asn Val Pro His His Gly Leu Tyr Glu Lys Glu Ile Val
          210          215          220
Ser His Leu Leu Thr Phe Ser Ser Phe Ser Lys Pro Ser Val Pro Gly
          225          230          235          240
Phe Cys Lys Cys Cys Ile Ser Ala Glu Asn Pro Arg Cys Leu Leu Leu
          245          250          255
Pro Pro Pro Val His Leu Glu Leu Cys Lys Asp Ser Ala Ser Val Phe
          260          265          270
Leu Ser Ser Ser Gly Pro Arg Val Ser Val
          275          280

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<210> 171

<211> 942

<212> DNA

<213> Homo sapiens

<400> 171

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caggctgatt ctggaagtgc tgaggaaaag cagctttaca acaaataccc agatgctgtg 120
gccacatggc taaaccctga cccatctcag aagcagaatc tcctagcccc acagaatgct 180
gtgtcctctg aagaaaccaa tgacttttaa caagagaccc ttccaagtaa gtccaacgaa 240
agccatgacc acatggatga tatggatgat gaagatgatg atgaccatgt ggacagccag 300
gactccattg actcgaacga ctctgatgat gtagatgaca ctgatgattc tcaccagtct 360
gatgagtctc accatttctga tgaatctgat gaactgggtc ctgattttcc cacggacctg 420
ccagcaaccg aagtttttcac tccagttgtc cccacagtag acacatatga tggccgaggt 480
gatagtgtgg tttatggact gaggtcaaaa tctaagaagt ttcgcagacc tgacatccag 540
taccctgatg ctacagacga gcacatcacc tcacacatgg aaagcgagga gttgaatggg 600
gcatacaagg ccatccccgt tgcccaggac ctgaacgcgc cttctgattg ggacagccgt 660
gggaaggaca gttatgaaac gagtcagctg gatgaccaga gtgctgaagc ccacagccac 720
aagcagtcca gattatataa gcggaaagct aatgatgaga gcaatgagca ttccgatgtg 780
attgatagtc aggaactttc caaagtcagc cgtgaattcc acagccatga atttcacagc 840
catgaagata tgctggttgt agaccccaaa agtaaggaag aagataaaca cctgaaattt 900
cgtatttctc atgaattaga tagtgcattc tctgaggtca at 942

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<210> 172

<211> 314

<212> PRT

<213> Homo sapiens

<400> 172

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Met Arg Ile Ala Val Ile Cys Phe Cys Leu Leu Gly Ile Thr Cys Ala
  1           5           10           15
Ile Pro Val Lys Gln Ala Asp Ser Gly Ser Ser Glu Glu Lys Gln Leu
          20           25           30
Tyr Asn Lys Tyr Pro Asp Ala Val Ala Thr Trp Leu Asn Pro Asp Pro
          35           40           45
Ser Gln Lys Gln Asn Leu Leu Ala Pro Gln Asn Ala Val Ser Ser Glu
          50           55           60
Glu Thr Asn Asp Phe Lys Gln Glu Thr Leu Pro Ser Lys Ser Asn Glu
        65           70           75           80
Ser His Asp His Met Asp Asp Met Asp Asp Glu Asp Asp Asp Asp His
          85           90           95
Val Asp Ser Gln Asp Ser Ile Asp Ser Asn Asp Ser Asp Asp Val Asp
          100          105          110
Asp Thr Asp Asp Ser His Gln Ser Asp Glu Ser His His Ser Asp Glu
          115          120          125
Ser Asp Glu Leu Val Thr Asp Phe Pro Thr Asp Leu Pro Ala Thr Glu
          130          135          140
Val Phe Thr Pro Val Val Pro Thr Val Asp Thr Tyr Asp Gly Arg Gly
        145          150          155          160
Asp Ser Val Val Tyr Gly Leu Arg Ser Lys Ser Lys Lys Phe Arg Arg
          165          170          175
Pro Asp Ile Gln Tyr Pro Asp Ala Thr Asp Glu His Ile Thr Ser His
          180          185          190
Met Glu Ser Glu Glu Leu Asn Gly Ala Tyr Lys Ala Ile Pro Val Ala
          195          200          205
Gln Asp Leu Asn Ala Pro Ser Asp Trp Asp Ser Arg Gly Lys Asp Ser
          210          215          220
Tyr Glu Thr Ser Gln Leu Asp Asp Gln Ser Ala Glu Ala His Ser His
        225          230          235          240
Lys Gln Ser Arg Leu Tyr Lys Arg Lys Ala Asn Asp Glu Ser Asn Glu
          245          250          255
His Ser Asp Val Ile Asp Ser Gln Glu Leu Ser Lys Val Ser Arg Glu
          260          265          270

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<400> 173						
gcagagcaca	gcatcgtcgg	gaccagactc	gtctcaggcc	agttgcagcc	ttctcagcca	60
aacgccgacc	aaggaaaact	cactaccatg	agaattgcag	tgattttgctt	ttgcctccta	120
ggcatcacct	gtgccatacc	agttaaacag	gctgattctg	gaagttctga	ggaaaagcag	180
ctttacaaca	aatacccaga	tgctgtggcc	acatggctaa	accctgaccc	atctcagaag	240
cagaatctcc	tagccccaca	gacccttcca	agtaagtcca	acgaaagcca	tgaccacatg	300
gatgatatgg	atgatgaaga	tgatgatgac	catgtggaca	gccaggactc	cattgactcg	360
aacgactctg	atgatgtaga	tgacactgat	gattctcacc	agtctgatga	gtctcaccat	420
tctgatgaat	ctgatgaact	ggtcactgat	tttcccacgg	acctgccagc	aaccgaagtt	480
ttcactccag	ttgtccccac	agtagacaca	tatgatggcc	gaggtgatag	tgtggtttat	540
ggactgaggt	caaaatctaa	gaagtttctg	agacctgaca	tccagtaccc	tgatgctaca	600
gacgaggaca	tcacctcaca	catggaaagc	gaggagttga	atggtgcata	caaggccatc	660
cccgttgccc	aggacctgaa	cgcgccttct	gattgggaca	gccgtgggaa	ggacagttat	720
gaaacgagtc	agctggatga	ccagagtgct	gaaaccacaca	gccacaagca	gtccagatta	780
tataagcgga	aagccaatga	tgagagcaat	gagcattccg	atgtgattga	tagtcaggaa	840
ctttccaaag	tcagccgtga	attccacagc	catgaatttc	acagccatga	agatatgctg	900
gttgtagacc	ccaaaagtaa	ggaagaagat	aaacacctga	aatttctgtat	ttctcatgaa	960
ttagatagtg	catcttctga	ggtcaattaa	aaggagaaaa	aatacaattt	ctcactttgc	1020
atttagtcaa	aagaaaaaat	gcttttatagc	aaaatgaaag	agaacatgaa	atgctttctt	1080
ctcagtttat	tggttgaatg	tgtatctatt	tgagtctgga	aataactaat	gtgtttgata	1140
attagtttag	tttgtggctt	catggaaact	ccctgtaaac	taaaagcttc	agggttatgt	1200
ctatgttcat	tctatagaag	aatgcaaac	tatcactgta	ttttaatat	tgttattctc	1260
tcatgaatag	aaatttatgt	agaagcaaac	aaaatacttt	taccacttta	aaaagagaat	1320
ataacatttt	atgtcactat	aatcttttgt	tttttaagtt	agtgtatat	ttgttgtgat	1380
tatctttttg	tgggtgtgaat	aatcttttta	tcttgaatgt	aataagaatt	tgggtggtgtc	1440
aattgcttat	ttgttttccc	acggttgtcc	agcaattaat	aaaacataac	cttttttact	1500
gcctaaaaaa	aaaaaaaaaa	aaaa				1524

```

<400> 174
Met Arg Ile Ala Val Ile Cys Phe Cys Leu Leu Gly Ile Thr Cys Ala
 1             5             10             15
Ile Pro Val Lys Gln Ala Asp Ser Gly Ser Ser Glu Glu Lys Gln Leu
      20             25             30
Tyr Asn Lys Tyr Pro Asp Ala Val Ala Thr Trp Leu Asn Pro Asp Pro
      35             40             45
Ser Gln Lys Gln Asn Leu Leu Ala Pro Gln Thr Leu Pro Ser Lys Ser
      50             55             60
Asn Glu Ser His Asp His Met Asp Asp Met Asp Asp Glu Asp Asp Asp
65             70             75             80
Asp His Val Asp Ser Gln Asp Ser Ile Asp Ser Asn Asp Ser Asp Asp
      85             90             95

```

Val	Asp	Asp	Thr	Asp	Asp	Ser	His	Gln	Ser	Asp	Glu	Ser	His	His	Ser
			100					105					110		
Asp	Glu	Ser	Asp	Glu	Leu	Val	Thr	Asp	Phe	Pro	Thr	Asp	Leu	Pro	Ala
		115					120					125			
Thr	Glu	Val	Phe	Thr	Pro	Val	Val	Pro	Thr	Val	Asp	Thr	Tyr	Asp	Gly
	130						135				140				
Arg	Gly	Asp	Ser	Val	Val	Tyr	Gly	Leu	Arg	Ser	Lys	Ser	Lys	Lys	Phe
145					150					155					160
Arg	Arg	Pro	Asp	Ile	Gln	Tyr	Pro	Asp	Ala	Thr	Asp	Glu	Asp	Ile	Thr
			165					170						175	
Ser	His	Met	Glu	Ser	Glu	Glu	Leu	Asn	Gly	Ala	Tyr	Lys	Ala	Ile	Pro
		180						185					190		
Val	Ala	Gln	Asp	Leu	Asn	Ala	Pro	Ser	Asp	Trp	Asp	Ser	Arg	Gly	Lys
	195						200					205			
Asp	Ser	Tyr	Glu	Thr	Ser	Gln	Leu	Asp	Asp	Gln	Ser	Ala	Glu	Thr	His
	210					215					220				
Ser	His	Lys	Gln	Ser	Arg	Leu	Tyr	Lys	Arg	Lys	Ala	Asn	Asp	Glu	Ser
225					230					235					240
Asn	Glu	His	Ser	Asp	Val	Ile	Asp	Ser	Gln	Glu	Leu	Ser	Lys	Val	Ser
			245						250					255	
Arg	Glu	Phe	His	Ser	His	Glu	Phe	His	Ser	His	Glu	Asp	Met	Leu	Val
		260					265						270		
Val	Asp	Pro	Lys	Ser	Lys	Glu	Glu	Asp	Lys	His	Leu	Lys	Phe	Arg	Ile
	275						280					285			
Ser	His	Glu	Leu	Asp	Ser	Ala	Ser	Ser	Glu	Val	Asn				
	290					295					300				

<210> 175

<211> 861

<212> DNA

<213> Homo sapiens

<400> 175

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caggctgatt ctggaagttc tgaggaaaag cagaatgctg tgtcctctga agaaaccaat 120
gacttttaaac aagagaccct tccaagtaag tccaacgaaa gccatgacca catggatgat 180
atggatgatg aagatgatga tgaccatgtg gacagccagg actccattga ctcgaacgac 240
tctgatgatg tagatgacac tgatgattct caccagtctg atgagtctca ccattctgat 300
gaatctgatg aactgggtcac tgattttccc acggacctgc cagcaaccga agttttcact 360
ccagttgtcc ccacagtaga cacatatgat ggccgagggtg atagtgtggt ttatggactg 420
aggtcaaaat ctaagaagtt tcgcagacct gacatccagt accctgatgc tacagacgag 480
cacatcacct cacacatgga aagcgaggag ttgaatggtg catacaaggc catccccgtt 540
gcccaggacc tgaacgcgcc ttctgattgg gacagccgtg ggaaggacag ttatgaaacg 600
agtcagctgg atgaccagag tgctgaagcc cacagccaca agcagtccag attatataag 660
cggaaagcta atgatgagag caatgagcat tccgatgtga ttgatagtca ggaactttcc 720
aaagtcagcc gtgaattcca cagccatgaa tttcacagcc atgaagatat gctggttgta 780
gaccccaaaa gtaaggaaga agataaacac ctgaaatttc gtattttctca tgaattagat 840
agtgcattct ctgaggtcaa t                                     861

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<210> 176

<211> 287

<212> PRT

<213> Homo sapiens

<400> 176

Met	Arg	Ile	Ala	Val	Ile	Cys	Phe	Cys	Leu	Leu	Gly	Ile	Thr	Cys	Ala
1				5					10					15	
Ile	Pro	Val	Lys	Gln	Ala	Asp	Ser	Gly	Ser	Ser	Glu	Glu	Lys	Gln	Asn

245

			20					25					30				
Ala	Val	Ser	Ser	Glu	Glu	Thr	Asn	Asp	Phe	Lys	Gln	Glu	Thr	Leu	Pro		
		35					40					45					
Ser	Lys	Ser	Asn	Glu	Ser	His	Asp	His	Met	Asp	Asp	Met	Asp	Asp	Glu		
	50					55					60						
Asp	Asp	Asp	Asp	His	Val	Asp	Ser	Gln	Asp	Ser	Ile	Asp	Ser	Asn	Asp		
65					70					75					80		
Ser	Asp	Asp	Val	Asp	Asp	Thr	Asp	Asp	Ser	His	Gln	Ser	Asp	Glu	Ser		
			85						90					95			
His	His	Ser	Asp	Glu	Ser	Asp	Glu	Leu	Val	Thr	Asp	Phe	Pro	Thr	Asp		
			100					105					110				
Leu	Pro	Ala	Thr	Glu	Val	Phe	Thr	Pro	Val	Val	Pro	Thr	Val	Asp	Thr		
		115					120					125					
Tyr	Asp	Gly	Arg	Gly	Asp	Ser	Val	Val	Tyr	Gly	Leu	Arg	Ser	Lys	Ser		
	130					135					140						
Lys	Lys	Phe	Arg	Arg	Pro	Asp	Ile	Gln	Tyr	Pro	Asp	Ala	Thr	Asp	Glu		
145					150				155						160		
His	Ile	Thr	Ser	His	Met	Glu	Ser	Glu	Glu	Leu	Asn	Gly	Ala	Tyr	Lys		
			165					170					175				
Ala	Ile	Pro	Val	Ala	Gln	Asp	Leu	Asn	Ala	Pro	Ser	Asp	Trp	Asp	Ser		
			180				185						190				
Arg	Gly	Lys	Asp	Ser	Tyr	Glu	Thr	Ser	Gln	Leu	Asp	Asp	Gln	Ser	Ala		
		195					200					205					
Glu	Ala	His	Ser	His	Lys	Gln	Ser	Arg	Leu	Tyr	Lys	Arg	Lys	Ala	Asn		
	210					215					220						
Asp	Glu	Ser	Asn	Glu	His	Ser	Asp	Val	Ile	Asp	Ser	Gln	Glu	Leu	Ser		
225					230				235						240		
Lys	Val	Ser	Arg	Glu	Phe	His	Ser	His	Glu	Phe	His	Ser	His	Glu	Asp		
			245						250					255			
Met	Leu	Val	Val	Asp	Pro	Lys	Ser	Lys	Glu	Glu	Asp	Lys	His	Leu	Lys		
			260					265					270				
Phe	Arg	Ile	Ser	His	Glu	Leu	Asp	Ser	Ala	Ser	Ser	Glu	Val	Asn			
		275					280					285					

<210> 177

<211> 3213

<212> DNA

<213> Homo sapiens

<400> 177

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agagactcaa gatgattccc tttttaccca tgttttctct actattgctg cttattgtta 60
accctataaa cgccaacaat cattatgaca agatcttggc tcatagtcgt atcaggggtc 120
gggaccaagg cccaaatgtc tgtgcccttc aacagatttt gggcaccaaa aagaaatact 180
tcagcacttg taagaactgg tataaaaagt ccatctgtgg acagaaaacg actgttttat 240
atgaatgttg ccctgggttat atgagaatgg aaggaatgaa aggctgcca gcagttttgc 300
ccattgacca tgttttatggc actctgggca tcgtgggagc caccacaacg cagcgctatt 360
ctgacgcctc aaaactgagg gaggagatcg agggaaaggg atccttcact tactttgcac 420
cgagtaatga ggcttgggac aacttggatt ctgatatccg tagaggtttg gagagcaacg 480
tgaatgttga attactgaat gctttacata gtcacatgat taataagaga atgttgacca 540
aggacttaaa aaatggcatg attattcctt caatgtataa caatttgggg cttttcatta 600
accattatcc taatgggggtt gtcactgtta attgtgctcg aatcatccat gggaaccaga 660
ttgcaacaaa tgggtgttgc catgtcattg accgtgtgct tacacaaatt ggtacctcaa 720
ttcaagactt cattgaagca gaagatgacc tttcatcttt tagagcagct gccatcacat 780
cggacatatt ggaggccctt ggaagagacg gtcacttcac actctttgct cccaccaatg 840
aggcttttga gaaacttcca cgaggtgtcc tagaaagggt catgggagac aaagtggctt 900
ccgaagctct tatgaagtac cacatcttaa atactctcca gtgttctgag tctattatgg 960
gaggagcagt ctttgagacg ctggaaggaa atacaattga gataggatgt gacggtgaca 1020
gtataacagt aaatggaatc aaaatggtga acaaaaagga tattgtgaca aataatggtg 1080

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tgatccattt gattgatcag gtcctaattc ctgatttctgc caaacaagtt attgagctgg 1140
ctggaaaaca gcaaaccacc ttcacggatc ttgtggccca attaggcttg gcatctgctc 1200
tgaggccaga tggagaatac acttttgctgg cacctgtgaa taatgcattt tctgatgata 1260
ctctcagcat ggttcagcgc ctcccttaaat taattctgca gaatcacata ttgaaagtaa 1320
aagttggcct taatgagctt tacaacgggc aaatactgga aaccatcgga ggcaaacagc 1380
tcagagtctt cgtatatcgt acagctgtct gcattgaaaa ttcattgcatg gagaaaggga 1440
gtaagcaagg gagaaacggg gcgattcaca tattccgcga gatcatcaag ccagcagaga 1500
aatccctcca tgaaaagtta aaacaagata agcgcttttag caccttcctc agcctacttg 1560
aagctgcaga cttgaaagag ctccctgacac aacctggaga ctggacatta tttgtgccaa 1620
ccaatgatgc ttttaaggga atgactagtg aagaaaaaga aattctgata cgggacaaaa 1680
atgctcttca aaacatcatt ctttatcacc tgacaccagg agtttttcatt ggaaaaggat 1740
ttgaacctgg tgttactaac attttaaaaga ccacacaagg aagcaaaatc tttctgaaag 1800
aagtaaatga tacacttctg gtgaatgaat tgaaatcaaa agaactctgac atcatgacaa 1860
caaatgggtg aattcatgtt gtagataaac tcctctatcc agcagacaca cctgttggaa 1920
atgatcaact gctggaaata cttaataaat taatcaaata catccaaatt aagtttggtc 1980
gtggtagcac cttcaaagaa atccccgtga ctgtctatac aactaaaatt ataaccaag 2040
ttgtggaacc aaaaattaaa gtgattgaag gcagtcttca gcctattatc aaaactgaag 2100
gaccacact aacaaaagtc aaaattgaag gtgaacctga attcagactg attaaagaag 2160
gtgaaacaat aactgaagtg atccatggag agccaattat taaaaaatac accaaaatca 2220
ttgatggagt gcctgtggaa ataactgaaa aagagacacg agaagaacga atcattacag 2280
gtcctgaaat aaaatacact aggatttcta ctggagggtg agaaacagaa gaaactctga 2340
agaaattggt acaagaagag gtcaccaagg tcaccaaat cattgaagggt ggtgatggtc 2400
atttatttga agatgaagaa attaaaagac tgcttcaggg agacacaccc gtgaggaagt 2460
tgcaagccaa caaaaaagtt caaggttcta gaagacgatt aagggaagggt cgttctcagt 2520
gaaaatccaa aaaccagaaa aaaatgttta tacaacccta agtcaataac ctgaccttag 2580
aaaattgtga gagccaagtt gacttcagga actgaaacat cagcacaag aagcaatcat 2640
caaataattc tgaacacaaa tttaatat ttttttctga atgagaaaca tgagggaaat 2700
tgtggagtta gcctcctgtg gtaaaggaat tgaagaaaat ataacacctt acaccctttt 2760
tcatcttgac attaaaagtt ctggctaact ttggaatcca ttagagaaaa atccttgtca 2820
ccagattcat tacaattcaa atcgaagagt tgtgaactgt tatcccattg aaaagaccga 2880
gccttgtatg tatgttatgg atacataaaa tgcacgcaag ccattatctc tccatgggaa 2940
gctaagttat aaaaataggt gcttggtgta caaaactttt tatatcaaaa ggctttgcac 3000
atttctatat gagtgggttt actggtaaat tatgttat tttaacaacta attttgtact 3060
ctcagaatgt ttgtcatatg cttcttgcaa tgcataat ttaatctcaa acgtttcaat 3120
aaaaccattt ttcagatata aagagaatta cttcaaattg agtaattcag aaaaactcaa 3180
gatttaagtt aaaaagtggt ttggacttgg gaa 3213

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<210> 178

<211> 836

<212> PRT

<213> Homo sapiens

<400> 178

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Met Ile Pro Phe Leu Pro Met Phe Ser Leu Leu Leu Leu Ile Val
 1           5           10          15
Asn Pro Ile Asn Ala Asn Asn His Tyr Asp Lys Ile Leu Ala His Ser
          20          25          30
Arg Ile Arg Gly Arg Asp Gln Gly Pro Asn Val Cys Ala Leu Gln Gln
          35          40          45
Ile Leu Gly Thr Lys Lys Lys Tyr Phe Ser Thr Cys Lys Asn Trp Tyr
          50          55          60
Lys Lys Ser Ile Cys Gly Gln Lys Thr Thr Val Leu Tyr Glu Cys Cys
65          70          75          80
Pro Gly Tyr Met Arg Met Glu Gly Met Lys Gly Cys Pro Ala Val Leu
          85          90          95
Pro Ile Asp His Val Tyr Gly Thr Leu Gly Ile Val Gly Ala Thr Thr
          100         105         110
Thr Gln Arg Tyr Ser Asp Ala Ser Lys Leu Arg Glu Glu Ile Glu Gly
          115         120         125

```


Lys	Gly	Ser	Phe	Thr	Tyr	Phe	Ala	Pro	Ser	Asn	Glu	Ala	Trp	Asp	Asn
130						135					140				
Leu	Asp	Ser	Asp	Ile	Arg	Arg	Gly	Leu	Glu	Ser	Asn	Val	Asn	Val	Glu
145					150					155					160
Leu	Leu	Asn	Ala	Leu	His	Ser	His	Met	Ile	Asn	Lys	Arg	Met	Leu	Thr
			165						170					175	
Lys	Asp	Leu	Lys	Asn	Gly	Met	Ile	Ile	Pro	Ser	Met	Tyr	Asn	Asn	Leu
			180					185					190		
Gly	Leu	Phe	Ile	Asn	His	Tyr	Pro	Asn	Gly	Val	Val	Thr	Val	Asn	Cys
		195					200					205			
Ala	Arg	Ile	Ile	His	Gly	Asn	Gln	Ile	Ala	Thr	Asn	Gly	Val	Val	His
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<212> DNA

<213> Homo sapiens

<400> 179

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<211> 779

<212> PRT

<213> Homo sapiens

<400> 180

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Pro	Gly	Val	Ile	Arg	Leu	Leu	Asp	Trp	Phe	Glu	Thr	Gln	Glu	Gly	Phe
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Met	Leu	Val	Leu	Glu	Arg	Pro	Leu	Pro	Ala	Gln	Asp	Leu	Phe	Asp	Tyr
		115					120					125			
Ile	Thr	Glu	Lys	Gly	Pro	Leu	Gly	Glu	Gly	Pro	Ser	Arg	Cys	Phe	Phe
	130					135					140				
Gly	Gln	Val	Val	Ala	Ala	Ile	Gln	His	Cys	His	Ser	Arg	Gly	Val	Val
145					150					155					160
His	Arg	Asp	Ile	Lys	Asp	Glu	Asn	Ile	Leu	Ile	Asp	Leu	Arg	Arg	Gly
				165					170					175	
Cys	Ala	Lys	Leu	Ile	Asp	Phe	Gly	Ser	Gly	Ala	Leu	Leu	His	Asp	Glu
			180					185					190		
Pro	Tyr	Thr	Asp	Phe	Asp	Gly	Thr	Arg	Val	Tyr	Ser	Pro	Pro	Glu	Trp
		195				200						205			
Ile	Ser	Arg	His	Gln	Tyr	His	Ala	Leu	Pro	Ala	Thr	Val	Trp	Ser	Leu
	210					215					220				
Gly	Ile	Leu	Leu	Tyr	Asp	Met	Val	Cys	Gly	Asp	Ile	Pro	Phe	Glu	Arg
225					230					235					240
Asp	Gln	Glu	Ile	Leu	Glu	Ala	Glu	Leu	His	Phe	Pro	Ala	His	Val	Ser
				245					250					255	
Pro	Asp	Cys	Cys	Ala	Leu	Ile	Arg	Arg	Cys	Leu	Ala	Pro	Lys	Pro	Ser
			260					265					270		
Ser	Arg	Pro	Ser	Leu	Glu	Glu	Ile	Leu	Leu	Asp	Pro	Trp	Met	Gln	Thr
		275					280					285			
Pro	Ala	Glu	Asp	Val	Thr	Pro	Gln	Pro	Leu	Gln	Arg	Arg	Pro	Cys	Pro
	290					295					300				
Phe	Gly	Leu	Val	Leu	Ala	Thr	Leu	Ser	Leu	Ala	Trp	Pro	Gly	Leu	Ala
305					310					315					320
Pro	Asn	Gly	Gln	Lys	Ser	His	Pro	Met	Ala	Met	Ser	Gln	Gly		
				325					330						

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<210> 183
<211> 2304
<212> DNA
<213> Homo sapiens
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<400> 183

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gagcgactcc aaaggcagca atgaacttca tcaagttcca tcgaactgtg actgtctaaa 180
tggaggaaca tgtgtgtcca acaagtactt ctccaacatt cactgggtgca actgccc aaa 240
gaaattcgga gggcagcact gtgaaataga taagtcaaaa acctgctatg aggggaatgg 300
tcactttttac cgaggaaagg ccagcactga caccatgggc cggccctgcc tgccttgga 360
ctctgccact gtccttcagc aaacgtacca tgcccacaga tctgatgctc ttcagctggg 420
cctggggaaa cataattact gcaggaaacc agacaaccgg aggcgaccct ggtgctatgt 480
gcaggtgggc ctaaagccgc ttgtccaaga gtgcatgggt catgactgcg cagatggaaa 540
aaagccctcc tctcctccag aagaattaaa atttcagtgt ggccaaaaga ctctgaggcc 600
ccgctttaag attattgggg gagaattcac caccatcgag aaccagccct ggtttgcggc 660
catctacagg aggcaccggg ggggctctgt cacctacgtg tgtggaggca gcctcatcag 720
cccttgctgg gtgatcagcg ccacacactg cttcattgat tacc aaaga agaggacta 780
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caccacaaa atgctatgtg ctgctgacct ccaatggaaa acagattcct gccagggaga 1200
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attccatgaa tgtatcagga aatataatg tgtgtgtatg tttgcacact tgttgtgtgg 1920
gctgtgagtg taagtgtgag taagagctgg tgtctgattg ttaagtctaa atatttcctt 1980
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acctgtgacc agcactgtct cagtttcact ttcacataga tgtccctttc ttggccagtt 2160
atcccttctt tttagcctag ttcattccaat cctcactggg tgggggtgagg accactcctt 2220
aactgaata tttatatatt actattttta tttatatatt tgtaatttta aataaaagt 2280
atcaataaaa tgtgattttt ctga 2304

```

<210> 184

<211> 431

<212> PRT

<213> Homo sapiens

<400> 184

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Met Arg Ala Leu Leu Ala Arg Leu Leu Leu Cys Val Leu Val Val Ser
 1      5      10      15
Asp Ser Lys Gly Ser Asn Glu Leu His Gln Val Pro Ser Asn Cys Asp
      20      25      30
Cys Leu Asn Gly Gly Thr Cys Val Ser Asn Lys Tyr Phe Ser Asn Ile
      35      40      45
His Trp Cys Asn Cys Pro Lys Lys Phe Gly Gly Gln His Cys Glu Ile
      50      55      60
Asp Lys Ser Lys Thr Cys Tyr Glu Gly Asn Gly His Phe Tyr Arg Gly
      65      70      75      80
Lys Ala Ser Thr Asp Thr Met Gly Arg Pro Cys Leu Pro Trp Asn Ser
      85      90      95

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Ala	Thr	Val	Leu	Gln	Gln	Thr	Tyr	His	Ala	His	Arg	Ser	Asp	Ala	Leu
			100					105					110		
Gln	Leu	Gly	Leu	Gly	Lys	His	Asn	Tyr	Cys	Arg	Asn	Pro	Asp	Asn	Arg
		115					120					125			
Arg	Arg	Pro	Trp	Cys	Tyr	Val	Gln	Val	Gly	Leu	Lys	Pro	Leu	Val	Gln
	130					135					140				
Glu	Cys	Met	Val	His	Asp	Cys	Ala	Asp	Gly	Lys	Lys	Pro	Ser	Ser	Pro
145					150					155					160
Pro	Glu	Glu	Leu	Lys	Phe	Gln	Cys	Gly	Gln	Lys	Thr	Leu	Arg	Pro	Arg
			165					170						175	
Phe	Lys	Ile	Ile	Gly	Gly	Glu	Phe	Thr	Thr	Ile	Glu	Asn	Gln	Pro	Trp
		180					185						190		
Phe	Ala	Ala	Ile	Tyr	Arg	Arg	His	Arg	Gly	Gly	Ser	Val	Thr	Tyr	Val
	195					200						205			
Cys	Gly	Gly	Ser	Leu	Ile	Ser	Pro	Cys	Trp	Val	Ile	Ser	Ala	Thr	His
	210					215					220				
Cys	Phe	Ile	Asp	Tyr	Pro	Lys	Lys	Glu	Asp	Tyr	Ile	Val	Tyr	Leu	Gly
225					230					235					240
Arg	Ser	Arg	Leu	Asn	Ser	Asn	Thr	Gln	Gly	Glu	Met	Lys	Phe	Glu	Val
			245					250						255	
Glu	Asn	Leu	Ile	Leu	His	Lys	Asp	Tyr	Ser	Ala	Asp	Thr	Leu	Ala	His
		260					265						270		
His	Asn	Asp	Ile	Ala	Leu	Leu	Lys	Ile	Arg	Ser	Lys	Glu	Gly	Arg	Cys
	275						280					285			
Ala	Gln	Pro	Ser	Arg	Thr	Ile	Gln	Thr	Ile	Cys	Leu	Pro	Ser	Met	Tyr
	290					295					300				
Asn	Asp	Pro	Gln	Phe	Gly	Thr	Ser	Cys	Glu	Ile	Thr	Gly	Phe	Gly	Lys
305					310					315					320
Glu	Asn	Ser	Thr	Asp	Tyr	Leu	Tyr	Pro	Glu	Gln	Leu	Lys	Met	Thr	Val
			325						330					335	
Val	Lys	Leu	Ile	Ser	His	Arg	Glu	Cys	Gln	Gln	Pro	His	Tyr	Tyr	Gly
		340						345					350		
Ser	Glu	Val	Thr	Thr	Lys	Met	Leu	Cys	Ala	Ala	Asp	Pro	Gln	Trp	Lys
	355						360					365			
Thr	Asp	Ser	Cys	Gln	Gly	Asp	Ser	Gly	Gly	Pro	Leu	Val	Cys	Ser	Leu
	370					375					380				
Gln	Gly	Arg	Met	Thr	Leu	Thr	Gly	Ile	Val	Ser	Trp	Gly	Arg	Gly	Cys
385					390					395					400
Ala	Leu	Lys	Asp	Lys	Pro	Gly	Val	Tyr	Thr	Arg	Val	Ser	His	Phe	Leu
			405					410						415	
Pro	Trp	Ile	Arg	Ser	His	Thr	Lys	Glu	Glu	Asn	Gly	Leu	Ala	Leu	
		420						425					430		

<210> 185
 <211> 2123
 <212> DNA
 <213> Homo sapiens

<400> 185
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 gccgggggtcc ccggagttgc agctcccgga gctccggcgg cggtccacc ggcgaaagag 180
 atcccggagg tcctagtggg cccacgcagc cggcggcgct atgtgcgggg ccgctttttg 240
 ggcaagggcg gctttgccaa gtgcttcgag atctcggacg cggacaccaa ggaggtgttc 300
 gcgggcaaga ttgtgcctaa gtctctgctg ctcaagccgc accagaggga gaagatgtcc 360
 atggaaatat ccattcaccg cagcctcgcc caccagcacg tcgtaggatt ccacggcttt 420
 ttcgaggaca acgacttcgt gttcgtggtg ttggagctct gccgccggag gtctctcctg 480
 gagccgcaca agaggaggaa agccctgact gagcctgagg cccgatacta cctacggcaa 540


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attgtgcttg gctgccagta cctgcaccga aaccgagtta ttcacgcaga cctcaagctg 600
ggcaaccttt tcctgaatga agatctggag gtgaaaatag gggatttttg actggcaacc 660
aaagtcgaat atgacgggga gaggaagaag accctgtgtg ggactcctaa ttacatagct 720
cccgaggtgc tgagcaagaa agagcacagt ttcgaggtgg atgtgtggtc cattgggtgt 780
atcatgtata ccttgttagt gggcaaacca ccttttgaga cttcttgccct aaaagagacc 840
tacctccgga tcaagaagaa tgaatacagt attcccaagc acatcaaccc cgtggccgcc 900
tccctcatcc agaagatgct tcagacagat ccactgccc gcccaaccat taacgagctg 960
cttaatgacg agttctttac ttctggctat atccctgccc gtctcccat cacctgcctg 1020
accattccac caaggttttc gattgctccc agcagcctgg accccagcaa ccggaagccc 1080
ctcacagtcc tcaataaagg cttggagaac ccctgcctg agcgtccccg ggaaaaagaa 1140
gaaccagtgg ttcgagagac aggtgaggtg gtcgactgcc acctcagtga catgctgcag 1200
cagctgcaca gtgtcaatgc ctccaagccc tcggagcgtg ggctggtcag gcaagaggag 1260
gctgaggatc ctgcctgcat ccccatcttc tgggtcagca agtgggtgga ctattcggac 1320
aagtacggcc ttgggtatca gctctgtgat aacagcgtgg ggggtgctctt caatgactca 1380
acacgcctca tcctctacaa tgatggtgac agcctgcagt acatagagcg tgacggcact 1440
gagtcctacc tcaccgtgag ttcccatccc aactccttga tgaagaagat caccctcctt 1500
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cgcaagggtg atgagctcgc ccggctgccc tacctacgga cctgggtccg caccgcagc 1620
gccatcatcc tgcacctcag caacggcagc gtgcagatca acttcttcca ggatcacacc 1680
aagctcatct tgtgccact gatggcagcc gtgacctaca tcgacgagaa gcgggacttc 1740
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catctggggc ccatactggt tggctcccgc ggtgccatgt ctgcagtgtg cccccagcc 1980
ccggtggctg ggcagagctg catcatcctt gcagggtggg gttgctgtat aagttatattt 2040
tgtacatgtt cgggtgtggg ttctacagac ttgtccccct cccctcaac cccaccatat 2100
gaattgtaca gaatatattct att 2123

```

<210> 186

<211> 603

<212> PRT

<213> Homo sapiens

<400> 186

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Met Ser Ala Ala Val Thr Ala Gly Lys Leu Ala Arg Ala Pro Ala Asp
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Pro Gly Lys Ala Gly Val Pro Gly Val Ala Ala Pro Gly Ala Pro Ala
          20          25          30
Ala Ala Pro Pro Ala Lys Glu Ile Pro Glu Val Leu Val Asp Pro Arg
          35          40          45
Ser Arg Arg Arg Tyr Val Arg Gly Arg Phe Leu Gly Lys Gly Gly Phe
          50          55          60
Ala Lys Cys Phe Glu Ile Ser Asp Ala Asp Thr Lys Glu Val Phe Ala
65          70          75          80
Gly Lys Ile Val Pro Lys Ser Leu Leu Leu Lys Pro His Gln Arg Glu
          85          90          95
Lys Met Ser Met Glu Ile Ser Ile His Arg Ser Leu Ala His Gln His
          100          105          110
Val Val Gly Phe His Gly Phe Phe Glu Asp Asn Asp Phe Val Phe Val
          115          120          125
Val Leu Glu Leu Cys Arg Arg Arg Ser Leu Leu Glu Pro His Lys Arg
          130          135          140
Arg Lys Ala Leu Thr Glu Pro Glu Ala Arg Tyr Tyr Leu Arg Gln Ile
145          150          155          160
Val Leu Gly Cys Gln Tyr Leu His Arg Asn Arg Val Ile His Arg Asp
          165          170          175
Leu Lys Leu Gly Asn Leu Phe Leu Asn Glu Asp Leu Glu Val Lys Ile
          180          185          190
Gly Asp Phe Gly Leu Ala Thr Lys Val Glu Tyr Asp Gly Glu Arg Lys

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<400> 187

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aagcagtctc aagcctgccg cagggagaag atggcggtcg ccgtgagaac tttgcaggaa 60
cagctggaag aggccaaaga gagtcttaag aacgtggatg agaacattcg caagctcacc 120
gggcggggacc cgaatgatgt gagggccatc caagccagat tgctggccct ttctggtcct 180
ggtggaggta gaggacgtgg tagttttattg ctgaggcggtg gattctcaga tagtggagga 240
ccccagcca aacagagaga ccttgaaggg gcagtcagta ggctgggcgg ggagcgtcgg 300
accagaagag aatcacgcca ggaaagcgac ccggaggatg atgatgttaa aaagccagca 360
ttgcagtctt cagttgtagc tacctccaaa gagcgcacac gtagagacct tatccaggat 420
caaaatatgg atgaaaaggg aaagcaaagg aaccgacgaa tatttggctt attgatgggc 480
actcttcaga aatttaaaca agaatccact gttgctactg aaaggcaaaa caggcgccag 540
gaaattgaac aaaaacttga agtgcaggcg gaagaagaaa gaaagcagggt tgaaaatgaa 600
aggagagaac tgtttgaaga gaggcgtgct aaacagacag aactgcggct tttagaacag 660
aaggttgagc ttgcgcagct gcaagaagaa tggaatgaac ataatgcaa aataattaaa 720
tatataagaa ctaagacaaa gccccatttg ttttatattc ccggaagaat gtgtccagct 780
acccaaaaac taatagaaga gtcacagaga aaaatgaacg ctttatattg tggtagacgc 840
atcgaatttg cagaacaaat aaataaaatg gaggctaggc ctagaagaca atcaatgaag 900
gaaaaagagc atcaggtggt gcgtaatgaa gaacacaagg cggaacaaga agagggttag 960
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atggttgaga atgtcaaaca tgtaattgct gaccaggagg taatggaaac taatcgagtt 1260
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cgaactagaa atagaaccac caagagtaga agtcgaagca gtagcagtag cagttctagt 1860
agcagttcaa ccagtagcag cagtggaggt agttccagca gtggaagtag tagcagtcgc 1920
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tccgacagaa agaggtctat atcagagagt agtcgatcag gcaaaagatc ttcaagaagt 2220
gaaagagacc gaaatcaga caggaaagac aaaaggcggt aatggaagaa gccaggcttt 2280
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gaggatgctg ccttaagaat tgcagtgtgt aaaaaatctt tttggaagat acagactgtt 2400
tgtttaccag acattcttgt actttttgca taattttgta agagttattt atcaaaatta 2460
tgtgaggttc caaaatatgt aaaaatgata ataataaaaa aagattaaca tcccttgta 2520
tcttttttaa atatcctata ctcttcagta agaattctgt tattttaata ggcaaattct 2580
taagtctgtt cccttcaatt ctgtatcata cattgct 2617

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<210> 188

<211> 743

<212> PRT

<213> Homo sapiens

<400> 188

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Met Ala Val Ala Val Arg Thr Leu Gln Glu Gln Leu Glu Lys Ala Lys
 1             5             10             15
Glu Ser Leu Lys Asn Val Asp Glu Asn Ile Arg Lys Leu Thr Gly Arg
 20             25             30
Asp Pro Asn Asp Val Arg Pro Ile Gln Ala Arg Leu Leu Ala Leu Ser
 35             40             45
Gly Pro Gly Gly Gly Arg Gly Arg Gly Ser Leu Leu Leu Arg Arg Gly
 50             55             60

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Phe	Ser	Asp	Ser	Gly	Gly	Pro	Pro	Ala	Lys	Gln	Arg	Asp	Leu	Glu	Gly
65					70					75					80
Ala	Val	Ser	Arg	Leu	Gly	Gly	Glu	Arg	Arg	Thr	Arg	Arg	Glu	Ser	Arg
				85					90					95	
Gln	Glu	Ser	Asp	Pro	Glu	Asp	Asp	Asp	Val	Lys	Lys	Pro	Ala	Leu	Gln
			100					105					110		
Ser	Ser	Val	Val	Ala	Thr	Ser	Lys	Glu	Arg	Thr	Arg	Arg	Asp	Leu	Ile
		115					120					125			
Gln	Asp	Gln	Asn	Met	Asp	Glu	Lys	Gly	Lys	Gln	Arg	Asn	Arg	Arg	Ile
	130						135				140				
Phe	Gly	Leu	Leu	Met	Gly	Thr	Leu	Gln	Lys	Phe	Lys	Gln	Glu	Ser	Thr
145					150					155					160
Val	Ala	Thr	Glu	Arg	Gln	Asn	Arg	Arg	Gln	Glu	Ile	Glu	Gln	Lys	Leu
				165					170					175	
Glu	Val	Gln	Ala	Glu	Glu	Glu	Arg	Lys	Gln	Val	Glu	Asn	Glu	Arg	Arg
			180					185					190		
Glu	Leu	Phe	Glu	Glu	Arg	Arg	Ala	Lys	Gln	Thr	Glu	Leu	Arg	Leu	Leu
		195					200					205			
Glu	Gln	Lys	Val	Glu	Leu	Ala	Gln	Leu	Gln	Glu	Glu	Trp	Asn	Glu	His
	210					215					220				
Asn	Ala	Lys	Ile	Ile	Lys	Tyr	Ile	Arg	Thr	Lys	Thr	Lys	Pro	His	Leu
225					230					235					240
Phe	Tyr	Ile	Pro	Gly	Arg	Met	Cys	Pro	Ala	Thr	Gln	Lys	Leu	Ile	Glu
				245					250					255	
Glu	Ser	Gln	Arg	Lys	Met	Asn	Ala	Leu	Phe	Asp	Gly	Arg	Arg	Ile	Glu
			260					265					270		
Phe	Ala	Glu	Gln	Ile	Asn	Lys	Met	Glu	Ala	Arg	Pro	Arg	Arg	Gln	Ser
		275					280					285			
Met	Lys	Glu	Lys	Glu	His	Gln	Val	Val	Arg	Asn	Glu	Glu	His	Lys	Ala
	290					295					300				
Glu	Gln	Glu	Glu	Gly	Lys	Val	Ala	Gln	Arg	Glu	Glu	Glu	Leu	Val	Glu
305					310					315					320
Thr	Gly	Asn	Gln	His	Asn	Asp	Val	Glu	Ile	Glu	Glu	Ala	Gly	Glu	Glu
				325					330					335	
Glu	Glu	Lys	Glu	Ile	Gly	Ile	Val	His	Ser	Asp	Ala	Glu	Lys	Glu	Gln
			340					345					350		
Glu	Glu	Glu	Glu	Gln	Lys	Gln	Glu	Met	Glu	Val	Lys	Met	Glu	Glu	Glu
		355					360					365			
Thr	Glu	Val	Arg	Glu	Ser	Glu	Lys	Gln	Gln	Asp	Ser	Gln	Pro	Glu	Glu
	370					375					380				
Val	Met	Asp	Val	Leu	Glu	Met	Val	Glu	Asn	Val	Lys	His	Val	Ile	Ala
385					390					395					400
Asp	Gln	Glu	Val	Met	Glu	Thr	Asn	Arg	Val	Glu	Ser	Val	Glu	Pro	Ser
				405					410					415	
Glu	Asn	Glu	Ala	Ser	Lys	Glu	Leu	Glu	Pro	Glu	Met	Glu	Phe	Glu	Ile
			420					425					430		
Glu	Pro	Asp	Lys	Glu	Cys	Lys	Ser	Leu	Ser	Pro	Gly	Lys	Glu	Asn	Val
		435					440					445			
Ser	Ala	Leu	Asp	Met	Glu	Lys	Glu	Ser	Asp	Glu	Lys	Glu	Glu	Lys	Glu
					455					460					
Ser	Glu	Pro	Gln	Pro	Glu	Pro	Val	Ala	Gln	Pro	Gln	Ala	Gln	Ser	Gln
465					470					475					480
Pro	Gln	Leu	Gln	Leu	Gln	Ser	Gln	Ser	Glu	Pro	Gln	Pro	Gln	Leu	Gln
				485					490					495	
Pro	Glu	Pro	Ala	Gln	Pro	Gln	Leu	Gln	Ser	Gln	Pro	Gln	Leu	Gln	Leu
			500					505					510		
Gln	Ser	Gln	Cys	His	Ala	Val	Leu	Gln	Ser	His	Pro	Pro	Ser	Gln	Pro
		515					520					525			
Glu	Asp	Leu	Ser	Leu	Ala	Val	Leu	Gln	Pro	Thr	Pro	Gln	Val	Thr	Gln

530		535		540
Glu His Gly His Phe Leu Pro Glu Arg Lys Asp Phe Pro Val Glu Ser				
545		550		555
Val Lys Leu Thr Glu Val Pro Val Asp Pro Val Leu Thr Val His Pro				
	565		570	575
Glu Ser Glu Ser Glu Thr Asn Thr Arg Ser Arg Ser Arg Gly Arg Thr				
	580		585	590
Arg Asn Arg Thr Thr Lys Ser Arg Ser Arg Ser Ser Ser Ser Ser Ser				
	595		600	605
Ser Ser Ser Ser Ser Thr Ser Ser Ser Ser Gly Ser Ser Ser Ser Ser				
	610		615	620
Gly Ser Ser Ser Ser Arg Ser Ser Ser Ser Ser Ser Ser Ser Thr Ser				
625		630		635
Gly Ser Ser Ser Arg Asp Ser Ser Ser Ser Thr Ser Ser Ser Ser Glu				
	645		650	655
Ser Arg Ser Arg Ser Arg Gly Arg Gly His Asn Arg Asp Arg Lys His				
	660		665	670
Arg Arg Ser Val Asp Arg Lys Arg Arg Asp Thr Ser Gly Leu Glu Arg				
	675		680	685
Ser His Lys Ser Ser Lys Gly Gly Ser Ser Arg Asp Thr Lys Gly Ser				
	690		695	700
Lys Asp Lys Asn Ser Arg Ser Asp Arg Lys Arg Ser Ile Ser Glu Ser				
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Asp Arg Lys Asp Lys Arg Arg				
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<210> 189

<211> 1182

<212> DNA

<213> Homo sapiens

<400> 189

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<210> 190

<211> 158

<212> PRT

<213> Homo sapiens

<400> 190

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			20					25					30		
Ala	Arg	Tyr	Gln	Trp	Val	Arg	Cys	Asn	Pro	Asp	Ser	Asn	Ser	Ala	Asn
		35					40					45			
Cys	Leu	Glu	Glu	Lys	Gly	Pro	Met	Phe	Glu	Leu	Leu	Pro	Gly	Glu	Ser
	50					55					60				
Asn	Lys	Ile	Pro	Arg	Leu	Arg	Thr	Asp	Leu	Phe	Pro	Lys	Thr	Arg	Ile
65					70					75					80
Gln	Asp	Leu	Asn	Arg	Ile	Phe	Pro	Leu	Ser	Glu	Asp	Tyr	Ser	Gly	Ser
			85					90						95	
Gly	Phe	Gly	Ser	Gly	Ser	Gly	Ser	Gly	Ser	Gly	Ser	Gly	Ser	Gly	Phe
			100					105					110		
Leu	Thr	Glu	Met	Glu	Gln	Asp	Tyr	Gln	Leu	Val	Asp	Glu	Ser	Asp	Ala
		115					120					125			
Phe	His	Asp	Asn	Leu	Arg	Ser	Leu	Asp	Arg	Asn	Leu	Pro	Ser	Asp	Ser
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<210> 191

<211> 1595

<212> DNA

<213> Homo sapiens

<400> 191

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<210> 192
<211> 175
<212> PRT
<213> Homo sapiens

<400> 192
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20 25 30
Arg Leu Lys Arg Ala Val Ser Glu His Gln Leu Leu His Asp Lys Gly
35 40 45
Lys Ser Ile Gln Asp Leu Arg Arg Arg Phe Phe Leu His His Leu Ile
50 55 60
Ala Glu Ile His Thr Ala Glu Ile Arg Ala Thr Ser Glu Val Ser Pro
65 70 75 80
Asn Ser Lys Pro Ser Pro Asn Thr Lys Asn His Pro Val Arg Phe Gly
85 90 95
Ser Asp Asp Glu Gly Arg Tyr Leu Thr Gln Glu Thr Asn Lys Val Glu
100 105 110
Thr Tyr Lys Glu Gln Pro Leu Lys Thr Pro Gly Lys Lys Lys Lys Gly
115 120 125
Lys Pro Gly Lys Arg Lys Glu Gln Glu Lys Lys Lys Arg Arg Thr Arg
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145 150 155 160
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<210> 193
<211> 2657
<212> DNA
<213> Homo sapiens

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<210> 194

<211> 168

<212> PRT

<213> Homo sapiens

<400> 194

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20          25          30
Gly Lys Lys Glu Lys Pro Glu Lys Lys Val Lys Lys Ser Asp Cys Gly
35          40          45
Glu Trp Gln Trp Ser Val Cys Val Pro Thr Ser Gly Asp Cys Gly Leu
50          55          60
Gly Thr Arg Glu Gly Thr Arg Thr Gly Ala Glu Cys Lys Gln Thr Met
65          70          75          80
Lys Thr Gln Arg Cys Lys Ile Pro Cys Asn Trp Lys Lys Gln Phe Gly
85          90          95
Ala Glu Cys Lys Tyr Gln Phe Gln Ala Trp Gly Glu Cys Asp Leu Asn
100         105         110
Thr Ala Leu Lys Thr Arg Thr Gly Ser Leu Lys Arg Ala Leu His Asn
115         120         125
Ala Glu Cys Gln Lys Thr Val Thr Ile Ser Lys Pro Cys Gly Lys Leu
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Lys Lys Gln Glu Lys Met Leu Asp
165

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<210> 195

<211> 2972
<212> DNA
<213> Homo sapiens

<400> 195

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<210> 196
<211> 890
<212> PRT

<213> Homo sapiens

<400> 196

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Ser	Val	Val	Arg	Lys	Asn	Leu	Leu	Ser	Asp	Cys	Ser	Val	Val	Ser	Thr	35	40	45	
Ser	Leu	Glu	Asp	Lys	Gln	Gln	Val	Pro	Ser	Glu	Asp	Ser	Met	Glu	Lys	50	55	60	
Val	Lys	Val	Tyr	Leu	Arg	Val	Arg	Pro	Leu	Leu	Pro	Ser	Glu	Leu	Glu	65	70	75	80
Arg	Gln	Glu	Asp	Gln	Gly	Cys	Val	Arg	Ile	Glu	Asn	Val	Glu	Thr	Leu	85	90	95	
Val	Leu	Gln	Ala	Pro	Lys	Asp	Ser	Phe	Ala	Leu	Lys	Ser	Asn	Glu	Arg	100	105	110	
Gly	Ile	Gly	Gln	Ala	Thr	His	Arg	Phe	Thr	Phe	Ser	Gln	Ile	Phe	Gly	115	120	125	
Pro	Glu	Val	Gly	Gln	Ala	Ser	Phe	Phe	Asn	Leu	Thr	Val	Lys	Glu	Met	130	135	140	
Val	Lys	Asp	Val	Leu	Lys	Gly	Gln	Asn	Trp	Leu	Ile	Tyr	Thr	Tyr	Gly	145	150	155	160
Val	Thr	Asn	Ser	Gly	Lys	Thr	His	Thr	Ile	Gln	Gly	Thr	Ile	Lys	Asp	165	170	175	
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Phe	Asp	Ser	Gly	Ile	Ala	Gly	Leu	Ser	Ser	Ile	Ser	Gln	Cys	Thr	Ser	260	265	270	
Ser	Ser	Gln	Leu	Asp	Glu	Thr	Ser	His	Arg	Trp	Ala	Gln	Pro	Asp	Thr	275	280	285	
Ala	Pro	Leu	Pro	Val	Pro	Ala	Asn	Ile	Arg	Phe	Ser	Ile	Trp	Ile	Ser	290	295	300	
Phe	Phe	Glu	Ile	Tyr	Asn	Glu	Leu	Leu	Tyr	Asp	Leu	Leu	Glu	Pro	Pro	305	310	315	320
Ser	Gln	Gln	Arg	Lys	Arg	Gln	Thr	Leu	Arg	Leu	Cys	Glu	Asp	Gln	Asn	325	330	335	
Gly	Asn	Pro	Tyr	Val	Lys	Asp	Leu	Asn	Trp	Ile	His	Val	Gln	Asp	Ala	340	345	350	
Glu	Glu	Ala	Trp	Lys	Leu	Leu	Lys	Val	Gly	Arg	Lys	Asn	Gln	Ser	Phe	355	360	365	
Ala	Ser	Thr	His	Leu	Asn	Gln	Asn	Ser	Ser	Arg	Ser	His	Ser	Ile	Phe	370	375	380	
Ser	Ile	Arg	Ile	Leu	His	Leu	Gln	Gly	Glu	Gly	Asp	Ile	Val	Pro	Lys	385	390	395	400
Ile	Ser	Glu	Leu	Ser	Leu	Cys	Asp	Leu	Ala	Gly	Ser	Glu	Arg	Cys	Lys	405	410	415	
Asp	Gln	Lys	Ser	Gly	Glu	Arg	Leu	Lys	Glu	Ala	Gly	Asn	Ile	Asn	Thr	420	425	430	
Ser	Leu	His	Thr	Leu	Gly	Arg	Cys	Ile	Ala	Ala	Leu	Arg	Gln	Asn	Gln	435	440	445	

Gln	Asn	Arg	Ser	Lys	Gln	Asn	Leu	Val	Pro	Phe	Arg	Asp	Ser	Lys	Leu	
	450					455					460					
Thr	Arg	Val	Phe	Gln	Gly	Phe	Phe	Thr	Gly	Arg	Gly	Arg	Ser	Cys	Met	
465					470					475					480	
Ile	Val	Asn	Val	Asn	Pro	Cys	Ala	Ser	Thr	Tyr	Asp	Glu	Thr	Leu	His	
				485					490					495		
Val	Ala	Lys	Phe	Ser	Ala	Ile	Ala	Ser	Gln	Leu	Val	His	Ala	Pro	Pro	
			500					505					510			
Met	Gln	Leu	Gly	Phe	Pro	Ser	Leu	His	Ser	Phe	Ile	Lys	Glu	His	Ser	
		515					520					525				
Leu	Gln	Val	Ser	Pro	Ser	Leu	Glu	Lys	Gly	Ala	Lys	Ala	Asp	Thr	Gly	
	530					535					540					
Leu	Asp	Asp	Asp	Ile	Glu	Asn	Glu	Ala	Asp	Ile	Ser	Met	Tyr	Gly	Lys	
545					550					555					560	
Glu	Glu	Leu	Leu	Gln	Val	Val	Glu	Ala	Met	Lys	Thr	Leu	Leu	Leu	Lys	
				565					570					575		
Glu	Arg	Gln	Glu	Lys	Leu	Gln	Leu	Glu	Met	His	Leu	Arg	Asp	Glu	Ile	
			580					585					590			
Cys	Asn	Glu	Met	Val	Glu	Gln	Met	Gln	Gln	Arg	Glu	Gln	Trp	Cys	Ser	
	595					600						605				
Glu	His	Leu	Asp	Thr	Gln	Lys	Glu	Leu	Leu	Glu	Glu	Met	Tyr	Glu	Glu	
	610					615					620					
Lys	Leu	Asn	Ile	Leu	Lys	Glu	Ser	Leu	Thr	Ser	Phe	Tyr	Gln	Glu	Glu	
625					630					635					640	
Ile	Gln	Glu	Arg	Asp	Glu	Lys	Ile	Glu	Glu	Leu	Glu	Ala	Leu	Leu	Gln	
			645					650						655		
Glu	Ala	Arg	Gln	Gln	Ser	Val	Ala	His	Gln	Gln	Ser	Gly	Ser	Glu	Leu	
			660					665					670			
Ala	Leu	Arg	Arg	Ser	Gln	Arg	Leu	Ala	Ala	Ser	Ala	Ser	Thr	Gln	Gln	
	675					680						685				
Leu	Gln	Glu	Val	Lys	Ala	Lys	Leu	Gln	Gln	Cys	Lys	Ala	Glu	Leu	Asn	
	690					695					700					
Ser	Thr	Thr	Glu	Glu	Leu	His	Lys	Tyr	Gln	Lys	Met	Leu	Glu	Pro	Pro	
705					710					715					720	
Pro	Ser	Ala	Lys	Pro	Phe	Thr	Ile	Asp	Val	Asp	Lys	Lys	Leu	Glu	Glu	
			725					730						735		
Gly	Gln	Lys	Asn	Ile	Arg	Leu	Leu	Arg	Thr	Glu	Leu	Gln	Lys	Leu	Gly	
			740					745					750			
Glu	Ser	Leu	Gln	Ser	Ala	Glu	Arg	Ala	Cys	Cys	His	Ser	Thr	Gly	Ala	
	755					760						765				
Gly	Lys	Leu	Arg	Gln	Ala	Leu	Thr	Thr	Cys	Asp	Asp	Ile	Leu	Ile	Lys	
	770					775				780						
Gln	Asp	Gln	Thr	Leu	Ala	Glu	Leu	Gln	Asn	Asn	Met	Val	Leu	Val	Lys	
785					790					795					800	
Leu	Asp	Leu	Arg	Lys	Lys	Ala	Ala	Cys	Ile	Ala	Glu	Gln	Tyr	His	Thr	
			805					810						815		
Val	Leu	Lys	Leu	Gln	Gly	Gln	Val	Ser	Ala	Lys	Lys	Arg	Leu	Gly	Thr	
			820					825					830			
Asn	Gln	Glu	Asn	Gln	Gln	Pro	Asn	Gln	Gln	Pro	Pro	Gly	Lys	Lys	Pro	
	835					840						845				
Phe	Leu	Arg	Asn	Leu	Leu	Pro	Arg	Thr	Pro	Thr	Cys	Gln	Ser	Ser	Thr	
	850					855					860					
Asp	Cys	Ser	Pro	Tyr	Ala	Arg	Ile	Leu	Arg	Ser	Arg	Arg	Ser	Pro	Leu	
865					870					875					880	
Leu	Lys	Ser	Gly	Pro	Phe	Gly	Lys	Lys	Tyr							
			885						890							

<211> 768
 <212> DNA
 <213> Homo sapiens

<400> 197
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 gatggcttcg ccacaccaag agcccaaacc tggagacctg attgagattt tccgccttgg 120
 ctatgagcac tgggccctgt atataggaga tggctacgtg atccatctgg ctccccaag 180
 tgagtacccc ggggctggct cctccagtgt cttctcagtc ctgagcaaca gtgcagaggt 240
 gaaacggggg cgcttgaag atgtggtggg aggctgttgc tatcgggtca acaacagctt 300
 ggaccatgag taccaaccac ggcccgtgga ggtgatcatc agttctgcga aggagatggg 360
 tggtcagaag atgaagtaca gtattgtgag caggaactgt gagcactttg tcgcccagct 420
 gagatatggc aagtcccgtg gtaaacaggt ggaaaaggcc aagggtgaag tcggtgtggc 480
 cacggcgctt ggaatcctgg ttgttgctgg atgctctttt gcgattagga gatacaaaaa 540
 aaaagcaaca gcctgaagca gccacaaaat cctgtgttag aagcagctgt ggggggtcca 600
 gtggagatga gcctcccca tgcctccagc agcctgacct tcgtgccctg tctcaggcgt 660
 tctctagatc ctttcctctg tttccctctc tcgctggcaa aagtatgatc taattgaaac 720
 aagactgaag gatcaataaa cagccatctg ccccttcaaa aaaaaaaa 768

<210> 198
 <211> 164
 <212> PRT
 <213> Homo sapiens

<400> 198
 Met Ala Ser Pro His Gln Glu Pro Lys Pro Gly Asp Leu Ile Glu Ile
 1 5 10 15
 Phe Arg Leu Gly Tyr Glu His Trp Ala Leu Tyr Ile Gly Asp Gly Tyr
 20 25 30
 Val Ile His Leu Ala Pro Pro Ser Glu Tyr Pro Gly Ala Gly Ser Ser
 35 40 45
 Ser Val Phe Ser Val Leu Ser Asn Ser Ala Glu Val Lys Arg Gly Arg
 50 55 60
 Leu Glu Asp Val Val Gly Gly Cys Cys Tyr Arg Val Asn Asn Ser Leu
 65 70 75 80
 Asp His Glu Tyr Gln Pro Arg Pro Val Glu Val Ile Ile Ser Ser Ala
 85 90 95
 Lys Glu Met Val Gly Gln Lys Met Lys Tyr Ser Ile Val Ser Arg Asn
 100 105 110
 Cys Glu His Phe Val Ala Gln Leu Arg Tyr Gly Lys Ser Arg Cys Lys
 115 120 125
 Gln Val Glu Lys Ala Lys Val Glu Val Gly Val Ala Thr Ala Leu Gly
 130 135 140
 Ile Leu Val Val Ala Gly Cys Ser Phe Ala Ile Arg Arg Tyr Gln Lys
 145 150 155 160
 Lys Ala Thr Ala

<210> 199
 <211> 720
 <212> DNA
 <213> Homo sapiens

<400> 199
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 gctgtcccgg cagtctccag ccgtcccggc cgcttgtggc caaactggct ccagtcactc 120
 ccgaaatgcc agtcgacttc actgggtact ggaagatgtt ggtcaacgag aatttcgagg 180
 agtacctgcg cgccctcgac gtcaatgtgg ccttgcgcaa aatcgccaac ttgctgaagc 240


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cagacaaaga gatcgtgcag gacggtgacc atatgatcat ccgcacgctg agcactttta 300
ggaactacat catggacttc caagttggga aggagtttga ggaggatctg acaggcatag 360
atgaccgcaa gtgcatgaca acagtgcgct gggacggaga caagctccag tgtgtgcaga 420
agggtgagaa ggaggggctg ggctggaccc agtggatcga gggatgatgag ctgcacctag 480
agatgagagt ggaaggtgtg gtctgcaagc aagtattcaa gaaggtgcag tgaggcccaa 540
gcagacaacc ttgtcccaac caatcagcag gatgtgtgag ccaggatccc tctttgcaca 600
gcatgaggca aaaatgtcca gccaccoccta ggcattctgtt agcagagtct gtctcttggc 660
tttgtcactt ttccttttct taaaacaaag ccatgccaat aaagtgcact gtgttcaaaa 720

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<210> 200

<211> 135

<212> PRT

<213> Homo sapiens

<400> 200

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Met Pro Val Asp Phe Thr Gly Tyr Trp Lys Met Leu Val Asn Glu Asn
 1           5           10           15
Phe Glu Glu Tyr Leu Arg Ala Leu Asp Val Asn Val Ala Leu Arg Lys
      20           25           30
Ile Ala Asn Leu Leu Lys Pro Asp Lys Glu Ile Val Gln Asp Gly Asp
      35           40           45
His Met Ile Ile Arg Thr Leu Ser Thr Phe Arg Asn Tyr Ile Met Asp
      50           55           60
Phe Gln Val Gly Lys Glu Phe Glu Glu Asp Leu Thr Gly Ile Asp Asp
      65           70           75           80
Arg Lys Cys Met Thr Thr Val Ser Trp Asp Gly Asp Lys Leu Gln Cys
      85           90           95
Val Gln Lys Gly Glu Lys Glu Gly Arg Gly Trp Thr Gln Trp Ile Glu
      100          105          110
Gly Asp Glu Leu His Leu Glu Met Arg Val Glu Gly Val Val Cys Lys
      115          120          125
Gln Val Phe Lys Lys Val Gln
      130          135

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<210> 201

<211> 2383

<212> DNA

<213> Homo sapiens

<400> 201

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tgccctactac gtgctgccct gcgcccgcag ccatgtgccg caccctggcc gccttcccca 120
ccacctgcct ggagagagcc aaagagttca agacacgtct ggggatcttt cttcacaat 180
cagagctggg ctgcgatact gggagtactg gcaagtccga gtgggggcagt aaacacagca 240
aagagaatag aaacttctca gaagatgtgc tgggggtggag agagtgcgttc gacctgctgc 300
tgagcagtaa aaatggagtg gctgccttcc acgctttcct gaagacagag ttcagtgagg 360
agaacctgga gttctggctg gcctgtgagg agttcaagaa gatccgatca gctaccaagc 420
tggcctccag ggcacaccag atctttgagg agttcatttg cagtgaggcc cctaaagagg 480
tcaacattga ccatgagacc cgcgagctga cgaggatgaa cctgcagact gccacagcca 540
catgctttga tgcggctcag gggaagacac gtaccctgat ggagaaggac tcctaccac 600
gcttcctgaa gtcgcctgct taccgggacc tggctgcca agcctcagcc gcctctgcca 660
ctctgtccag ctgcagcctg gacgagccct cacacacctg agtctccacg gcagtgagga 720
agccagccgg gaagagaggt tgagtcaccc atccccgagg tggctgcccc tgtgtgggag 780
gcaggttctg caaagcaagt gcaagaggac aaaaaaaaaa aaaaaaaaaa aaaaaatgcg 840
ctccagcagc ctgtttggga agcagcagtc tctccttcag atactgtggg actcatgctg 900
gagaggagcc gccacttcc aggacctgtg aataagggct aatgatgagg gttggtgggg 960
ctctctgtgg ggcaaaaagg tggatatggg gttagcactg gctctcgttc tcaccggaga 1020

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aggaagtgtt ctagtgtggt ttaggaaaca tgtggataaa gggaaccatg aaaatgagag 1080
gaggaaagac atccagatca gctgttttgc ctgttgctca gttgactctg attgcatcct 1140
gttttcctaa ttcccagact gttctgggca cggaagggac cctggatgtg gagtcttccc 1200
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cactcctgtg tgtctgtcca gccttgcaagt catgtcaagg ccagcaagct gatgtgactc 1320
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tcttcctgga tgtgccctct ctgagttctg tgctgtctct tggaggcagg gccaggaga 1560
acaaagtgtg gaggcctcgg ggagtggctt ttccagctct catgccccgc agtgtggaac 1620
aaggcagaaa aggatcctag gaaataagtc tcttggcggg ccctgagagt cctgctgaaa 1680
tccagccagt gttttttgtg gtatgagaac aggcaaaaag agatgccccg agatagaagg 1740
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caggaccatg gcacccttag agtgcagaag ctggggggag aggctgcttc gaagggcagg 1860
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ggataatcaa cactgttctc tctgtaccat gagctcctcc aggagattat ttaagtgtat 2040
tgtatcattg gttttctgtg attgtcataa cattgttttt gttattgttg gtgctgttgt 2100
tatttattat tgtaatttca gtttgcctct actggagaat ctcagcaggg gtttcagcct 2160
gactgtctcc ctttctctac cagactctac ctctgaatgt gctgggaacc tcttgagacc 2220
tgtcaggaac tcctcactgt ttaaataattht atttattgtg acaaattggag ctggtttcct 2280
agatatgaat gatgtttgca atccccattht tcctgtttca gcatgttata ttcttataaa 2340
ataaaagcaa aagtcaaata tgaaaaaaa aaaaaaaaaaaa aaa 2383

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<210> 202

<211> 202

<212> PRT

<213> Homo sapiens

<400> 202

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Met Cys Arg Thr Leu Ala Ala Phe Pro Thr Thr Cys Leu Glu Arg Ala
 1          5          10          15
Lys Glu Phe Lys Thr Arg Leu Gly Ile Phe Leu His Lys Ser Glu Leu
          20          25          30
Gly Cys Asp Thr Gly Ser Thr Gly Lys Ser Glu Trp Gly Ser Lys His
          35          40          45
Ser Lys Glu Asn Arg Asn Phe Ser Glu Asp Val Leu Gly Trp Arg Glu
          50          55          60
Ser Phe Asp Leu Leu Leu Ser Ser Lys Asn Gly Val Ala Ala Phe His
          65          70          75          80
Ala Phe Leu Lys Thr Glu Phe Ser Glu Glu Asn Leu Glu Phe Trp Leu
          85          90          95
Ala Cys Glu Glu Phe Lys Lys Ile Arg Ser Ala Thr Lys Leu Ala Ser
          100          105          110
Arg Ala His Gln Ile Phe Glu Glu Phe Ile Cys Ser Glu Ala Pro Lys
          115          120          125
Glu Val Asn Ile Asp His Glu Thr Arg Glu Leu Thr Arg Met Asn Leu
          130          135          140
Gln Thr Ala Thr Ala Thr Cys Phe Asp Ala Ala Gln Gly Lys Thr Arg
          145          150          155          160
Thr Leu Met Glu Lys Asp Ser Tyr Pro Arg Phe Leu Lys Ser Pro Ala
          165          170          175
Tyr Arg Asp Leu Ala Ala Gln Ala Ser Ala Ala Ser Ala Thr Leu Ser
          180          185          190
Ser Cys Ser Leu Asp Glu Pro Ser His Thr
          195          200

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<210> 203

<211> 616
 <212> DNA
 <213> Homo sapiens

<400> 203
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 gccacagatc catgatgtgc agttctctgg agcaggcgct ggctgtgctg gtcactacct 120
 tccacaagta ctctgccaa gagggcgaca agttcaagct gagtaagggg gaaatgaagg 180
 aacttctgca caaggagctg cccagctttg tggggcattc cagagaacca tgtgctgtga 240
 gggccttccg agtccatctg tttaatcctg tcattggaga cttgagaaac cagagcccag 300
 aagggaaaag tgattgtccc aagatcacac agcactggag aaagtggatg aggaggggct 360
 gaagaagctg atgggcagcc tggatgagaa cagtgaccag caggtggact tccaggagta 420
 tgctgttttc ctggcactca tcactgtcat gtgcaatgac ttcttccagg gctgcccaga 480
 ccgaccctga agcagaactc ttgacttcct gccatggatc tcttgggccc aggactgttg 540
 atgcctttga gttttgtatt caataaactt tttttgtctg ttgaaaaaaaa aaaaaaaaaa 600
 aaaaaaaaaa aaaaaa 616

<210> 204
 <211> 96
 <212> PRT
 <213> Homo sapiens

<400> 204
 Met Met Cys Ser Ser Leu Glu Gln Ala Leu Ala Val Leu Val Thr Thr
 1 5 10 15
 Phe His Lys Tyr Ser Cys Gln Glu Gly Asp Lys Phe Lys Leu Ser Lys
 20 25 30
 Gly Glu Met Lys Glu Leu Leu His Lys Glu Leu Pro Ser Phe Val Gly
 35 40 45
 His Ser Arg Glu Pro Cys Ala Val Arg Ala Phe Arg Val His Leu Phe
 50 55 60
 Asn Pro Val Ile Gly Asp Leu Arg Asn Gln Ser Pro Glu Gly Lys Ser
 65 70 75 80
 Asp Cys Pro Lys Ile Thr Gln His Trp Arg Lys Trp Met Arg Arg Gly
 85 90 95

<210> 205
 <211> 428
 <212> DNA
 <213> Homo sapiens

<400> 205
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 ggcgctggct gtgctgggtca ctaccttcca caagtactcc tgccaagagg gcgacaagtt 120
 caagctgagt aagggggaaa tgaaggaact tctgcacaag gagctgcca gctttgtggg 180
 ggagaaagtg gatgaggagg ggctgaagaa gctgatgggc agcctggatg agaacagtga 240
 ccagcaggtg gacttccagg agtatgctgt tttcctggca ctcactactg tcatgtgcaa 300
 tgacttcttc cagggctgcc cagaccgacc ctgaagcaga actcttgact tcctgccatg 360
 gatctcttgg gcccaggact gttgatgcct ttgagttttg tattcaataa actttttttg 420
 tctgttga 428

<210> 206
 <211> 97
 <212> PRT
 <213> Homo sapiens

<400> 206
 Met Cys Ser Ser Leu Glu Gln Ala Leu Ala Val Leu Val Thr Thr Phe

270

1				5					10					15			
His	Lys	Tyr	Ser	Cys	Gln	Glu	Gly	Asp	Lys	Phe	Lys	Leu	Ser	Lys	Gly		
			20					25					30				
Glu	Met	Lys	Glu	Leu	Leu	His	Lys	Glu	Leu	Pro	Ser	Phe	Val	Gly	Glu		
		35					40					45					
Lys	Val	Asp	Glu	Glu	Gly	Leu	Lys	Lys	Leu	Met	Gly	Ser	Leu	Asp	Glu		
	50					55					60						
Asn	Ser	Asp	Gln	Gln	Val	Asp	Phe	Gln	Glu	Tyr	Ala	Val	Phe	Leu	Ala		
65					70					75					80		
Leu	Ile	Thr	Val	Met	Cys	Asn	Asp	Phe	Phe	Gln	Gly	Cys	Pro	Asp	Arg		
				85					90					95			

Pro

<210> 207
 <211> 799
 <212> DNA
 <213> Homo sapiens

<400> 207

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gtgctgtacc	aagagtttgc	tcctggctgc	tttgatgtca	gtgctgctac	tccacctctg	120
cggcgaatca	gaagcagcaa	gcaactttga	ctgctgtcct	ggatacacag	accgtattct	180
tcctcctaaa	tttattgtgg	gcttcacacg	gcagctggcc	aatgaaggct	gtgacatcaa	240
tgctatcatc	tttcacacaa	agaaaaagtt	gtctgtgtgc	gcaaatacaa	aacagacttg	300
ggtgaaatat	attgtgctgc	tcctcagtaa	aaaagtcaag	aacatgtaaa	aactgtggct	360
tttctggaat	ggaattggac	atagcccaag	aacagaaaga	accttgctgg	ggttggaggt	420
ttcacttgca	catcatggag	ggtttagtgc	ttatctaatt	tgtgcctcac	tggaacttgc	480
caattaatga	agttgattca	tattgcatca	tagtttgctt	tgtttaagca	tcacattaaa	540
gttaaactgt	attttatgtt	atttatagct	gtagggtttc	tgtgttttagc	tatttaatac	600
taattttcca	taagctattt	tggttttagtg	caaagtataa	aattatatatt	gggggggaat	660
aagattatat	ggactttctt	gcaagcaaca	agctattttt	taaaaaaact	atttaacatt	720
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cattaataag	acaaatatt					799

<210> 208
 <211> 96
 <212> PRT
 <213> Homo sapiens

<400> 208

Met	Cys	Cys	Thr	Lys	Ser	Leu	Leu	Leu	Ala	Ala	Leu	Met	Ser	Val	Leu
1				5					10					15	
Leu	Leu	His	Leu	Cys	Gly	Glu	Ser	Glu	Ala	Ala	Ser	Asn	Phe	Asp	Cys
			20					25					30		
Cys	Leu	Gly	Tyr	Thr	Asp	Arg	Ile	Leu	His	Pro	Lys	Phe	Ile	Val	Gly
		35					40					45			
Phe	Thr	Arg	Gln	Leu	Ala	Asn	Glu	Gly	Cys	Asp	Ile	Asn	Ala	Ile	Ile
	50					55					60				
Phe	His	Thr	Lys	Lys	Lys	Leu	Ser	Val	Cys	Ala	Asn	Pro	Lys	Gln	Thr
65					70					75					80
Trp	Val	Lys	Tyr	Ile	Val	Arg	Leu	Leu	Ser	Lys	Lys	Val	Lys	Asn	Met
				85					90					95	

<210> 209
 <211> 2133
 <212> DNA

<213> Homo sapiens

<400> 209

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gaagccctgc ctgatgagac agaggtggtg gaagaaactg tggcagaggt gactgaggta 180
tctgtgggag ctaatcctgt ccaggtggaa gtaggagaaat ttgatgatgg tgcagaggaa 240
accgaagagg aggtggtggc ggaaaatccc tgccagaacc accactgcaa acacggcaag 300
gtgtgcgagc tggatgagaa caacaccccc atgtgcgtgt gccaggaccc caccagctgc 360
ccagccccc a ttggcgagtt tgagaagggtg tgcagcaatg acaacaagac cttcgactct 420
tcctgccact tctttgccac aaagtgcacc ctggaggggca ccaagaaggg ccacaagctc 480
cacctggact acatcgggcc ttgcaaatac atccccctt gcctggactc tgagctgacc 540
gaattcccc tgcgcatgcg ggactggctc aagaacgtcc tggtcaccct gtatgagagg 600
gatgaggaca acaaccttct gactgagaag cagaagctgc gggatgaaga gatccatgag 660
aatgagaagc gcctggaggc aggagaccac cccgtggagc tgctggcccg ggacttcgag 720
aagaactata acatgtacat cttccctgta cactggcagt tcggccagct ggaccagcac 780
cccattgacg ggtacctctc ccacaccgag ctggctccac tgcgtgctcc cctcatcccc 840
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gccctggatg agtgggcccg ctgcttcggc atcaagcaga aggatatoga caaggatctt 960
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ctgaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaa 2133

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<210> 210

<211> 303

<212> PRT

<213> Homo sapiens

<400> 210

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Met Arg Ala Trp Ile Phe Phe Leu Leu Cys Leu Ala Gly Arg Ala Leu
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Ala Ala Pro Gln Gln Glu Ala Leu Pro Asp Glu Thr Glu Val Val Glu
          20           25           30
Glu Thr Val Ala Glu Val Thr Glu Val Ser Val Gly Ala Asn Pro Val
          35           40           45
Gln Val Glu Val Gly Glu Phe Asp Asp Gly Ala Glu Glu Thr Glu Glu
          50           55           60
Glu Val Val Ala Glu Asn Pro Cys Gln Asn His His Cys Lys His Gly
65           70           75           80
Lys Val Cys Glu Leu Asp Glu Asn Asn Thr Pro Met Cys Val Cys Gln
          85           90           95
Asp Pro Thr Ser Cys Pro Ala Pro Ile Gly Glu Phe Glu Lys Val Cys

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			100					105				110				
Ser	Asn	Asp	Asn	Lys	Thr	Phe	Asp	Ser	Ser	Cys	His	Phe	Phe	Ala	Thr	
		115					120					125				
Lys	Cys	Thr	Leu	Glu	Gly	Thr	Lys	Lys	Gly	His	Lys	Leu	His	Leu	Asp	
	130					135					140					
Tyr	Ile	Gly	Pro	Cys	Lys	Tyr	Ile	Pro	Pro	Cys	Leu	Asp	Ser	Glu	Leu	
145					150					155					160	
Thr	Glu	Phe	Pro	Leu	Arg	Met	Arg	Asp	Trp	Leu	Lys	Asn	Val	Leu	Val	
			165					170						175		
Thr	Leu	Tyr	Glu	Arg	Asp	Glu	Asp	Asn	Asn	Leu	Leu	Thr	Glu	Lys	Gln	
		180						185					190			
Lys	Leu	Arg	Val	Lys	Lys	Ile	His	Glu	Asn	Glu	Lys	Arg	Leu	Glu	Ala	
	195					200						205				
Gly	Asp	His	Pro	Val	Glu	Leu	Leu	Ala	Arg	Asp	Phe	Glu	Lys	Asn	Tyr	
	210				215						220					
Asn	Met	Tyr	Ile	Phe	Pro	Val	His	Trp	Gln	Phe	Gly	Gln	Leu	Asp	Gln	
225					230					235					240	
His	Pro	Ile	Asp	Gly	Tyr	Leu	Ser	His	Thr	Glu	Leu	Ala	Pro	Leu	Arg	
			245					250						255		
Ala	Pro	Leu	Ile	Pro	Met	Glu	His	Cys	Thr	Thr	Arg	Phe	Phe	Glu	Thr	
		260				265						270				
Cys	Asp	Leu	Asp	Asn	Asp	Lys	Tyr	Ile	Ala	Leu	Asp	Glu	Trp	Ala	Gly	
	275					280					285					
Cys	Phe	Gly	Ile	Lys	Gln	Lys	Asp	Ile	Asp	Lys	Asp	Leu	Val	Ile		
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<210> 211
 <211> 2228
 <212> DNA
 <213> Homo sapiens

<400> 211
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 cctactccta aagtgattgg tattgatctt ggcaccacct attgttctgt tggggtgttt 180
 tttcctggca caggaaaagt aaaggtgatt ccagatgaaa atgggcatat cagcataccc 240
 agcatgggtg cttttactga caatgatgta tatgtgggat atgaaagcgt agagctggca 300
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 gcagaagagt tggaggctga aattggcaga taccatttta aggtttttaa caaaaatgga 420
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 aatgctgtca tttctgtacc agcagaattt gatctaaaac agagaaattc aacaattgaa 600
 gctgctaacc ttgcaggact gaagattttt agggtaataa atgaaccac agcagcagct 660
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 ccatttatca gattaccttt tccacaaaag aaagtctcta aaatatcaca gatttaccta 1560

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tgcatttg                                     2228

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<210> 212

<211> 471

<212> PRT

<213> Homo sapiens

<400> 212

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          20          25          30
Val Ile Gly Ile Asp Leu Gly Thr Thr Tyr Cys Ser Val Gly Val Phe
          35          40          45
Phe Pro Gly Thr Gly Lys Val Lys Val Ile Pro Asp Glu Asn Gly His
          50          55          60
Ile Ser Ile Pro Ser Met Val Ser Phe Thr Asp Asn Asp Val Tyr Val
65          70          75          80
Gly Tyr Glu Ser Val Glu Leu Ala Asp Ser Asn Pro Gln Asn Thr Ile
          85          90          95
Tyr Asp Ala Lys Arg Phe Ile Gly Lys Ile Phe Thr Ala Glu Glu Leu
          100          105          110
Glu Ala Glu Ile Gly Arg Tyr Pro Phe Lys Val Leu Asn Lys Asn Gly
          115          120          125
Met Val Glu Phe Ser Val Thr Ser Asn Glu Thr Ile Thr Val Ser Pro
          130          135          140
Glu Tyr Val Gly Ser Arg Leu Leu Leu Lys Leu Lys Glu Met Ala Glu
145          150          155          160
Ala Tyr Leu Gly Met Pro Val Ala Asn Ala Val Ile Ser Val Pro Ala
          165          170          175
Glu Phe Asp Leu Lys Gln Arg Asn Ser Thr Ile Glu Ala Ala Asn Leu
          180          185          190
Ala Gly Leu Lys Ile Leu Arg Val Ile Asn Glu Pro Thr Ala Ala Ala
          195          200          205
Met Ala Tyr Gly Leu His Lys Ala Asp Val Phe His Val Leu Val Ile
210          215          220
Asp Leu Gly Gly Gly Thr Leu Asp Val Ser Leu Leu Asn Lys Gln Gly
225          230          235          240
Gly Met Phe Leu Thr Arg Ala Met Ser Gly Asn Asn Lys Leu Gly Gly
          245          250          255
Gln Asp Phe Asn Gln Arg Leu Leu Gln Tyr Leu Tyr Lys Gln Ile Tyr
          260          265          270
Gln Thr Tyr Gly Phe Val Pro Ser Arg Lys Glu Glu Ile His Arg Leu
          275          280          285
Arg Gln Ala Val Glu Met Val Lys Leu Asn Leu Thr Leu His Gln Ser
290          295          300
Ala Gln Leu Ser Val Leu Leu Thr Val Glu Glu Gln Asp Arg Lys Glu
305          310          315          320

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Pro His Ser Ser Asp Thr Glu Leu Pro Lys Asp Lys Leu Ser Ser Ala
 325 330 335
 Asp Asp His Arg Val Asn Ser Gly Phe Gly Arg Gly Leu Ser Asp Lys
 340 345 350
 Lys Ser Gly Glu Ser Gln Val Leu Phe Glu Thr Glu Ile Ser Arg Lys
 355 360 365
 Leu Phe Asp Thr Leu Asn Glu Asp Leu Phe Gln Lys Ile Leu Val Pro
 370 375 380
 Ile Gln Gln Val Leu Lys Glu Gly His Leu Glu Lys Thr Glu Ile Asp
 385 390 395 400
 Glu Val Val Leu Val Gly Gly Ser Thr Arg Ile Pro Arg Ile Arg Gln
 405 410 415
 Val Ile Gln Glu Phe Phe Gly Lys Asp Pro Asn Thr Ser Val Asp Pro
 420 425 430
 Asp Leu Ala Val Val Thr Gly Val Ala Ile Gln Ala Gly Ile Asp Gly
 435 440 445
 Gly Ser Trp Pro Leu Gln Val Ser Ala Leu Glu Ile Pro Asn Lys His
 450 455 460
 Leu Gln Lys Thr Asn Phe Asn
 465 470

<210> 213
 <211> 1224
 <212> DNA
 <213> Homo sapiens

<400> 213
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 agcaccctgc cccagcagagt cctccggaaa gagcctgtca ccccatctgc acttgctcctc 180
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 ctgcgcagag agatcgaaat ccaggcccac ctgcaccatc ccaacatcct gcgtctctac 480
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 aagccagaaa atctgctctt agggctcaag ggagagctga agattgctga cttcggctgg 720
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 tctgtcgcct gatggctccct gtcattcact cgggtgcgtg tgtttgtatg tctgtgtatg 1140
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 ttaataaagg ctgaagcttt ttgt 1224

<210> 214
 <211> 344
 <212> PRT
 <213> Homo sapiens

<400> 214
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 Ala Pro Ser Gly Leu Ser Thr Leu Pro Gln Arg Val Leu Arg Lys Glu

275

			20					25				30				
Pro	Val	Thr	Pro	Ser	Ala	Leu	Val	Leu	Met	Ser	Arg	Ser	Asn	Val	Gln	
		35					40					45				
Pro	Thr	Ala	Ala	Pro	Gly	Gln	Lys	Val	Met	Glu	Asn	Ser	Ser	Gly	Thr	
	50					55					60					
Pro	Asp	Ile	Leu	Thr	Arg	His	Phe	Thr	Ile	Asp	Asp	Phe	Glu	Ile	Gly	
65					70					75					80	
Arg	Pro	Leu	Gly	Lys	Gly	Lys	Phe	Gly	Asn	Val	Tyr	Leu	Ala	Arg	Glu	
			85					90					95			
Lys	Lys	Ser	His	Phe	Ile	Val	Ala	Leu	Lys	Val	Leu	Phe	Lys	Ser	Gln	
		100					105					110				
Ile	Glu	Lys	Glu	Gly	Val	Glu	His	Gln	Leu	Arg	Arg	Glu	Ile	Glu	Ile	
	115					120						125				
Gln	Ala	His	Leu	His	His	Pro	Asn	Ile	Leu	Arg	Leu	Tyr	Asn	Tyr	Phe	
	130					135					140					
Tyr	Asp	Arg	Arg	Arg	Ile	Tyr	Leu	Ile	Leu	Glu	Tyr	Ala	Pro	Arg	Gly	
145					150					155					160	
Glu	Leu	Tyr	Lys	Glu	Leu	Gln	Lys	Ser	Cys	Thr	Phe	Asp	Glu	Gln	Arg	
			165					170					175			
Thr	Ala	Thr	Ile	Met	Glu	Glu	Leu	Ala	Asp	Ala	Leu	Met	Tyr	Cys	His	
		180					185					190				
Gly	Lys	Lys	Val	Ile	His	Arg	Asp	Ile	Lys	Pro	Glu	Asn	Leu	Leu	Leu	
	195					200						205				
Gly	Leu	Lys	Gly	Glu	Leu	Lys	Ile	Ala	Asp	Phe	Gly	Trp	Ser	Val	His	
	210					215					220					
Ala	Pro	Ser	Leu	Arg	Arg	Lys	Thr	Met	Cys	Gly	Thr	Leu	Asp	Tyr	Leu	
225					230					235					240	
Pro	Pro	Glu	Met	Ile	Glu	Gly	Arg	Met	His	Asn	Glu	Lys	Val	Asp	Leu	
			245					250					255			
Trp	Cys	Ile	Gly	Val	Leu	Cys	Tyr	Glu	Leu	Leu	Val	Gly	Asn	Pro	Pro	
		260					265					270				
Phe	Glu	Ser	Ala	Ser	His	Asn	Glu	Thr	Tyr	Arg	Arg	Ile	Val	Lys	Val	
	275					280						285				
Asp	Leu	Lys	Phe	Pro	Ala	Ser	Val	Pro	Thr	Gly	Ala	Gln	Asp	Leu	Ile	
	290					295				300						
Ser	Lys	Leu	Leu	Arg	His	Asn	Pro	Ser	Glu	Arg	Leu	Pro	Leu	Ala	Gln	
305					310					315					320	
Val	Ser	Ala	His	Pro	Trp	Val	Arg	Ala	Asn	Ser	Arg	Arg	Val	Leu	Pro	
			325					330					335			
Pro	Ser	Ala	Leu	Gln	Ser	Val	Ala									
		340														

<210> 215
 <211> 1421
 <212> DNA
 <213> Homo sapiens

<400> 215
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 caggtgatcc tcgggccgat gttctcagga aaaagcacag agttgatgag acgcgtccgt 180
 cgcttccaga ttgctcagta caagtgcctg gtgatcaagt atgccaaaga cactcgctac 240
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 gctgcactgg atgggacctt ccagagggaag ccatttgggg ccatacctgaa cctgggtgccg 480
 ctggccgaga gcgtgggtgaa gctgacggcg gtgtgcatgg agtgcttccg ggaagccgcc 540
 tataccaaga ggctcggcac agagaaggag gtcgaggtga ttggggggagc agacaagtac 600

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cactccgtgt gtcggctctg ctacttcaag aaggcctcag gccagcctgc cgggccggac 660
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<210> 216

<211> 234

<212> PRT

<213> Homo sapiens

<400> 216

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Thr Arg Gly Gln Ile Gln Val Ile Leu Gly Pro Met Phe Ser Gly Lys
      20           25           30
Ser Thr Glu Leu Met Arg Arg Val Arg Arg Phe Gln Ile Ala Gln Tyr
      35           40           45
Lys Cys Leu Val Ile Lys Tyr Ala Lys Asp Thr Arg Tyr Ser Ser Ser
      50           55           60
Phe Cys Thr His Asp Arg Asn Thr Met Glu Ala Leu Pro Ala Cys Leu
      65           70           75           80
Leu Arg Asp Val Ala Gln Glu Ala Leu Gly Val Ala Val Ile Gly Ile
      85           90           95
Asp Glu Gly Gln Phe Phe Pro Asp Ile Met Glu Phe Cys Glu Ala Met
      100          105          110
Ala Asn Ala Gly Lys Thr Val Ile Val Ala Ala Leu Asp Gly Thr Phe
      115          120          125
Gln Arg Lys Pro Phe Gly Ala Ile Leu Asn Leu Val Pro Leu Ala Glu
      130          135          140
Ser Val Val Lys Leu Thr Ala Val Cys Met Glu Cys Phe Arg Glu Ala
      145          150          155          160
Ala Tyr Thr Lys Arg Leu Gly Thr Glu Lys Glu Val Glu Val Ile Gly
      165          170          175
Gly Ala Asp Lys Tyr His Ser Val Cys Arg Leu Cys Tyr Phe Lys Lys
      180          185          190
Ala Ser Gly Gln Pro Ala Gly Pro Asp Asn Lys Glu Asn Cys Pro Val
      195          200          205
Pro Gly Lys Pro Gly Glu Ala Val Ala Ala Arg Lys Leu Phe Ala Pro
      210          215          220
Gln Gln Ile Leu Gln Cys Ser Pro Ala Asn
      225          230

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<210> 217

<211> 2307

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> 1691, 1698, 1705, 1708, 1709, 1713, 1717, 1720, 1724, 1728,
1733, 1741, 1746, 1748, 1755, 1770, 1774, 1791, 1802, 1821,
1838, 1856, 1859, 1864, 1908, 1959, 1997, 2012, 2038, 2143

<223> n = A,T,C or G

<400> 217

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<210> 218

<211> 428

<212> PRT

<213> Homo sapiens

<400> 218

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                20                25                30
Gly Ile Pro Ile Ile Ile Ala Leu Leu Ser Leu Ala Ser Ile Ile Ile
          35          40          45

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Val	Val	Val	Leu	Ile	Lys	Val	Ile	Leu	Asp	Lys	Tyr	Tyr	Phe	Leu	Cys
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Leu	Asp	Cys	Pro	Leu	Gly	Glu	Asp	Glu	Glu	His	Cys	Val	Lys	Ser	Phe
				85						90				95	
Pro	Glu	Gly	Pro	Ala	Val	Ala	Val	Arg	Leu	Ser	Lys	Asp	Arg	Ser	Thr
			100					105					110		
Leu	Gln	Val	Leu	Asp	Ser	Ala	Thr	Gly	Asn	Trp	Phe	Ser	Ala	Cys	Phe
		115					120					125			
Asp	Asn	Phe	Thr	Glu	Ala	Leu	Ala	Glu	Thr	Ala	Cys	Arg	Gln	Met	Gly
130						135					140				
Tyr	Ser	Ser	Lys	Pro	Thr	Phe	Arg	Ala	Val	Glu	Ile	Gly	Pro	Asp	Gln
145				150						155					160
Asp	Leu	Asp	Val	Val	Glu	Ile	Thr	Glu	Asn	Ser	Gln	Glu	Leu	Arg	Met
			165					170						175	
Arg	Asn	Ser	Ser	Gly	Pro	Cys	Leu	Ser	Gly	Ser	Leu	Val	Ser	Leu	His
			180					185					190		
Cys	Leu	Ala	Cys	Gly	Lys	Ser	Leu	Lys	Thr	Pro	Arg	Val	Val	Gly	Gly
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Glu	Glu	Ala	Ser	Val	Asp	Ser	Trp	Pro	Trp	Gln	Val	Ser	Ile	Gln	Tyr
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Asp	Lys	Gln	His	Val	Cys	Gly	Gly	Ser	Ile	Leu	Asp	Pro	His	Trp	Val
225				230						235					240
Leu	Thr	Ala	Ala	His	Cys	Phe	Arg	Lys	His	Thr	Asp	Val	Phe	Asn	Trp
			245					250						255	
Lys	Val	Arg	Ala	Gly	Ser	Asp	Lys	Leu	Gly	Ser	Phe	Pro	Ser	Leu	Ala
			260					265					270		
Val	Ala	Lys	Ile	Ile	Ile	Ile	Glu	Phe	Asn	Pro	Met	Tyr	Pro	Lys	Asp
	275						280				285				
Asn	Asp	Ile	Ala	Leu	Met	Lys	Leu	Gln	Phe	Pro	Leu	Thr	Phe	Ser	Gly
	290					295					300				
Thr	Val	Arg	Pro	Ile	Cys	Leu	Pro	Phe	Phe	Asp	Glu	Glu	Leu	Thr	Pro
305				310						315					320
Ala	Thr	Pro	Leu	Trp	Ile	Ile	Gly	Trp	Gly	Phe	Thr	Lys	Gln	Asn	Gly
			325					330						335	
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			340					345					350		
Ser	Thr	Arg	Cys	Asn	Ala	Asp	Asp	Ala	Tyr	Gln	Gly	Glu	Val	Thr	Glu
		355				360					365				
Lys	Met	Met	Cys	Ala	Gly	Ile	Pro	Glu	Gly	Gly	Val	Asp	Thr	Cys	Gln
	370					375					380				
Gly	Asp	Ser	Gly	Gly	Pro	Leu	Met	Tyr	Gln	Ser	Asp	Gln	Trp	His	Val
385				390						395					400
Val	Gly	Ile	Val	Ser	Trp	Gly	Tyr	Gly	Cys	Gly	Gly	Pro	Ser	Thr	Pro
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<210> 219

<211> 556

<212> DNA

<213> Homo sapiens

<400> 219

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 agtcgaaact gaagaagaca gagacgcaag agaaaaatcc actgccttcc aaagaaacga 180


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acaacgaagg ccgcgctgcc tttcccatct gtctatctat ctggctggca gggaaggaaa 420
gaacttgcac gttggtgaag gaagaagtgg ggtggaagaa gtggggtggg acgacagtga 480
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agtgccatth tttttt 556

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<210> 220

<211> 44

<212> PRT

<213> Homo sapiens

<400> 220

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Met Ser Asp Lys Pro Asp Met Ala Glu Ile Glu Lys Phe Asp Lys Ser
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          20          25          30
Glu Thr Ile Glu Gln Glu Lys Gln Ala Gly Glu Ser
      35          40

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<210> 221

<211> 4792

<212> DNA

<213> Homo sapiens

<400> 221

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tctgttgaaa gaatctatca aaagaaaaca caattggaac atattttgct ccgcccagac 180
acctacattg gttctgtgga attagtgacc cagcaaatgt gggtttacga tgaagatgtt 240
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ctagttaatg ctgcggacaa caaacaagg gacccaaaaa tgtcttgtat tagagtcaca 360
attgatccgg aaaacaattt aattagtata tggaataatg gaaaagggtat tcctgttggt 420
gaacacaaag ttgaaaagat gtatgtccca gctctcatat ttggacagct cctaacttct 480
agtaactatg atgatgatga aaagaaagt acaggtggtc gaaatggcta tggagccaaa 540
ttgtgtaaca tattcagtac caaatttact gtggaaacag ccagtagaga atacaagaaa 600
atgttcaaac agacatggat ggataatatg ggaagagctg gtgagatgga actcaagccc 660
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<210> 222

<211> 1531

<212> PRT

<213> Homo sapiens

<400> 222

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Ile	Tyr	Gln	Lys	Lys	Thr	Gln	Leu	Glu	His	Ile	Leu	Leu	Arg	Pro	Asp	
		35					40					45				
Thr	Tyr	Ile	Gly	Ser	Val	Glu	Leu	Val	Thr	Gln	Gln	Met	Trp	Val	Tyr	
	50					55					60					
Asp	Glu	Asp	Val	Gly	Ile	Asn	Tyr	Arg	Glu	Val	Thr	Phe	Val	Pro	Gly	
65					70					75					80	
Leu	Tyr	Lys	Ile	Phe	Asp	Glu	Ile	Leu	Val	Asn	Ala	Ala	Asp	Asn	Lys	
			85						90					95		
Gln	Arg	Asp	Pro	Lys	Met	Ser	Cys	Ile	Arg	Val	Thr	Ile	Asp	Pro	Glu	
			100					105					110			
Asn	Asn	Leu	Ile	Ser	Ile	Trp	Asn	Asn	Gly	Lys	Gly	Ile	Pro	Val	Val	
		115					120					125				
Glu	His	Lys	Val	Glu	Lys	Met	Tyr	Val	Pro	Ala	Leu	Ile	Phe	Gly	Gln	
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Leu	Leu	Thr	Ser	Ser	Asn	Tyr	Asp	Asp	Asp	Glu	Lys	Lys	Val	Thr	Gly	
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Gly	Arg	Asn	Gly	Tyr	Gly	Ala	Lys	Leu	Cys	Asn	Ile	Phe	Ser	Thr	Lys	
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Phe	Thr	Val	Glu	Thr	Ala	Ser	Arg	Glu	Tyr	Lys	Lys	Met	Phe	Lys	Gln	
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Thr	Trp	Met	Asp	Asn	Met	Gly	Arg	Ala	Gly	Glu	Met	Glu	Leu	Lys	Pro	
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Lys	Phe	Lys	Met	Gln	Ser	Leu	Asp	Lys	Asp	Ile	Val	Ala	Leu	Met	Val	
225					230					235					240	
Arg	Arg	Ala	Tyr	Asp	Ile	Ala	Gly	Ser	Thr	Lys	Asp	Val	Lys	Val	Phe	
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Met	Tyr	Leu	Lys	Asp	Lys	Leu	Asp	Glu	Thr	Gly	Asn	Ser	Leu	Lys	Val	
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Glu	Lys	Gly	Phe	Gln	Gln	Ile	Ser	Phe	Val	Asn	Ser	Ile	Ala	Thr	Ser	
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Lys	Gly	Gly	Arg	His	Val	Asp	Tyr	Val	Ala	Asp	Gln	Ile	Val	Thr	Lys	
			325						330					335		
Leu	Val	Asp	Val	Val	Lys	Lys	Lys	Asn	Lys	Gly	Gly	Val	Ala	Val	Lys	
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Ala	His	Gln	Val	Lys	Asn	His	Met	Trp	Ile	Phe	Val	Asn	Ala	Leu	Ile	
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Pro	Lys	Ser	Phe	Gly	Ser	Thr	Cys	Gln	Leu	Ser	Glu	Lys	Phe	Ile	Lys	
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Ala	Ala	Ile	Gly	Cys	Gly	Ile	Val	Glu	Ser	Ile	Leu	Asn	Trp	Val	Lys	
			405					410						415		
Phe	Lys	Ala	Gln	Val	Gln	Leu	Asn	Lys	Lys	Cys	Ser	Ala	Val	Lys	His	
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	450					455					460					
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Tyr	Gly	Val	Phe	Pro	Leu	Arg	Gly	Lys	Ile	Leu	Asn	Val	Arg	Glu	Ala	
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Ser	His	Lys	Gln	Ile	Met	Glu	Asn	Ala	Glu	Ile	Asn	Asn	Ile	Ile	Lys			
			500					505					510					
Ile	Val	Gly	Leu	Gln	Tyr	Lys	Lys	Asn	Tyr	Glu	Asp	Glu	Asp	Ser	Leu			
		515					520					525						
Lys	Thr	Leu	Arg	Tyr	Gly	Lys	Ile	Met	Ile	Met	Thr	Asp	Gln	Asp	Gln			
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Trp	Pro	Ser	Leu	Leu	Arg	His	Arg	Phe	Leu	Glu	Glu	Phe	Ile	Thr	Pro			
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		595				600					605							
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		675				680						685						
Thr	Thr	Thr	Tyr	Leu	Thr	Tyr	Asn	Asp	Phe	Ile	Asn	Lys	Glu	Leu	Ile			
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Glu	Met	Ser	Ser	Tyr	His	His	Gly	Glu	Met	Ser	Leu	Met	Met	Thr	Ile			
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785					790					795					800			
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			805					810						815				
Leu	Phe	Pro	Pro	Lys	Asp	Asp	His	Thr	Leu	Lys	Phe	Leu	Tyr	Asp	Asp			
			820					825					830					
Asn	Gln	Arg	Val	Glu	Pro	Glu	Trp	Tyr	Ile	Pro	Ile	Ile	Pro	Met	Val			
		835					840						845					
Leu	Ile	Asn	Gly	Ala	Glu	Gly	Ile	Gly	Thr	Gly	Trp	Ser	Cys	Lys	Ile			
		850				855					860							
Pro	Asn	Phe	Asp	Val	Arg	Glu	Ile	Val	Asn	Asn	Ile	Arg	Arg	Leu	Met			
865					870					875					880			
Asp	Gly	Glu	Glu	Pro	Leu	Pro	Met	Leu	Pro	Ser	Tyr	Lys	Asn	Phe	Lys			
			885					890						895				
Gly	Thr	Ile	Glu	Glu	Leu	Ala	Pro	Asn	Gln	Tyr	Val	Ile	Ser	Gly	Glu			
			900					905					910					
Val	Ala	Ile	Leu	Asn	Ser	Thr	Thr	Ile	Glu	Ile	Ser	Glu	Leu	Pro	Val			
		915					920						925					
Arg	Thr	Trp	Thr	Gln	Thr	Tyr	Lys	Glu	Gln	Val	Leu	Glu	Pro	Met	Leu			
		930				935					940							
Asn	Gly	Thr	Glu	Lys	Thr	Pro	Pro	Leu	Ile	Thr	Asp	Tyr	Arg	Glu	Tyr			
945					950					955					960			
His	Thr	Asp	Thr	Thr	Val	Lys	Phe	Val	Val	Lys	Met	Thr	Glu	Glu	Lys			

				965					970					975			
Leu	Ala	Glu	Ala	Glu	Arg	Val	Gly	Leu	His	Lys	Val	Phe	Lys	Leu	Gln		
			980					985					990				
Thr	Ser	Leu	Thr	Cys	Asn	Ser	Met	Val	Leu	Phe	Asp	His	Val	Gly	Cys		
		995					1000					1005					
Leu	Lys	Lys	Tyr	Asp	Thr	Val	Leu	Asp	Ile	Leu	Arg	Asp	Phe	Phe	Glu		
	1010					1015					1020						
Leu	Arg	Leu	Lys	Tyr	Tyr	Gly	Leu	Arg	Lys	Glu	Trp	Leu	Leu	Gly	Met		
1025					1030					1035					1040		
Leu	Gly	Ala	Glu	Ser	Ala	Lys	Leu	Asn	Asn	Gln	Ala	Arg	Phe	Ile	Leu		
				1045					1050					1055			
Glu	Lys	Ile	Asp	Gly	Lys	Ile	Ile	Ile	Glu	Asn	Lys	Pro	Lys	Lys	Glu		
			1060					1065					1070				
Leu	Ile	Lys	Val	Leu	Ile	Gln	Arg	Gly	Tyr	Asp	Ser	Asp	Pro	Val	Lys		
	1075						1080					1085					
Ala	Trp	Lys	Glu	Ala	Gln	Gln	Lys	Val	Pro	Asp	Glu	Glu	Glu	Asn	Glu		
	1090					1095					1100						
Glu	Ser	Asp	Asn	Glu	Lys	Glu	Thr	Glu	Lys	Ser	Asp	Ser	Val	Thr	Asp		
1105					1110					1115					1120		
Ser	Gly	Pro	Thr	Phe	Asn	Tyr	Leu	Leu	Asp	Met	Pro	Leu	Trp	Tyr	Leu		
				1125					1130					1135			
Thr	Lys	Glu	Lys	Lys	Asp	Glu	Leu	Cys	Arg	Leu	Arg	Asn	Glu	Lys	Glu		
			1140					1145					1150				
Gln	Glu	Leu	Asp	Thr	Leu	Lys	Arg	Lys	Ser	Pro	Ser	Asp	Leu	Trp	Lys		
	1155					1160					1165						
Glu	Asp	Leu	Ala	Thr	Phe	Ile	Glu	Glu	Leu	Glu	Ala	Val	Glu	Ala	Lys		
	1170					1175					1180						
Glu	Lys	Gln	Asp	Glu	Gln	Val	Gly	Leu	Pro	Gly	Lys	Gly	Gly	Lys	Ala		
1185					1190					1195					1200		
Lys	Gly	Lys	Lys	Thr	Gln	Met	Ala	Glu	Val	Leu	Pro	Ser	Pro	Arg	Gly		
				1205					1210					1215			
Gln	Arg	Val	Ile	Pro	Arg	Ile	Thr	Ile	Glu	Met	Lys	Ala	Glu	Ala	Glu		
			1220					1225					1230				
Lys	Lys	Asn	Lys	Lys	Lys	Ile	Lys	Asn	Glu	Asn	Thr	Glu	Gly	Ser	Pro		
	1235					1240					1245						
Gln	Glu	Asp	Gly	Val	Glu	Leu	Glu	Gly	Leu	Lys	Gln	Arg	Leu	Glu	Lys		
	1250					1255					1260						
Lys	Gln	Lys	Arg	Glu	Pro	Gly	Thr	Lys	Thr	Lys	Lys	Gln	Thr	Thr	Leu		
1265					1270					1275					1280		
Ala	Phe	Lys	Pro	Ile	Lys	Lys	Gly	Lys	Lys	Arg	Asn	Pro	Trp	Pro	Asp		
				1285					1290					1295			
Ser	Glu	Ser	Asp	Arg	Ser	Ser	Asp	Glu	Ser	Asn	Phe	Asp	Val	Pro	Pro		
			1300					1305					1310				
Arg	Glu	Thr	Glu	Pro	Arg	Arg	Ala	Ala	Thr	Lys	Thr	Lys	Phe	Thr	Met		
	1315						1320						1325				
Asp	Leu	Asp	Ser	Asp	Glu	Asp	Phe	Ser	Asp	Phe	Asp	Glu	Lys	Thr	Asp		
	1330					1335					1340						
Asp	Glu	Asp	Phe	Val	Pro	Ser	Asp	Ala	Ser	Pro	Pro	Lys	Thr	Lys	Thr		
1345					1350					1355					1360		
Ser	Pro	Lys	Leu	Ser	Asn	Lys	Glu	Leu	Lys	Pro	Gln	Lys	Ser	Val	Val		
				1365					1370					1375			
Ser	Asp	Leu	Glu	Ala	Asp	Asp	Val	Lys	Gly	Ser	Val	Pro	Leu	Ser	Ser		
			1380					1385					1390				
Ser	Pro	Pro	Ala	Thr	His	Phe	Pro	Asp	Glu	Thr	Glu	Ile	Thr	Asn	Pro		
	1395						1400						1405				
Val	Pro	Lys	Lys	Asn	Val	Thr	Val	Lys	Lys	Thr	Ala	Ala	Lys	Ser	Gln		
	1410					1415					1420						
Ser	Ser	Thr	Ser	Thr	Thr	Gly	Ala	Lys	Lys	Arg	Ala	Ala	Pro	Lys	Gly		
1425					1430					1435					1440		

Thr Lys Arg Asp Pro Ala Leu Asn Ser Gly Val Ser Gln Lys Pro Asp
 1445 1450 1455
 Pro Ala Lys Thr Lys Asn Arg Arg Lys Arg Lys Pro Ser Thr Ser Asp
 1460 1465 1470
 Asp Ser Asp Ser Asn Phe Glu Lys Ile Val Ser Lys Ala Val Thr Ser
 1475 1480 1485
 Lys Lys Ser Lys Gly Glu Ser Asp Asp Phe His Met Asp Phe Asp Ser
 1490 1495 1500
 Ala Val Ala Pro Arg Ala Lys Ser Val Arg Ala Lys Lys Pro Ile Lys
 1505 1510 1515 1520
 Tyr Leu Glu Glu Ser Asp Glu Asp Asp Leu Phe
 1525 1530

<210> 223
 <211> 1111
 <212> DNA
 <213> Homo sapiens

<400> 223
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 acgccatcaa gaagaagatg cagatgctga agctcgacaa ggagaacgcc ttggatcgag 120
 ctgagcaggc ggaggccgac aagaaggcgg cggaagacag gagcaagcag ctggaagatg 180
 agctggtgtc actgcaaaag aaactcaagg gcaccgaaga tgaactggac aaataactctg 240
 aggctctcaa agatgcccag gagaagctgg agctggcaga gaaaaaggcc accgatgctg 300
 aagccgacgt agcttctctg aacagacgca tccagctggt tgaggaagag ttggatcggt 360
 cccaggagcg tctggcaaca gctttgcaga agctggagga agctgagaag gcagcagatg 420
 agagtgagag aggcatgaaa gtcattgaga gtcgagccca aaaagatgaa gaaaaaatgg 480
 aaattcagga gatccaactg aaagaggcca agcacattgc tgaagatgcc gaccgcaaatt 540
 acgaagaggt ggcccgttaag ctggtcatca ttgagagcga cctggaacgt gcagaggagc 600
 gggctgagct ctcagaaggc aaatgtgccg agcttgaaga agaattgaaa actgtgacga 660
 acaacttgaa gtcactggag gctcaggctg agaagtactc gcagaaggaa gacagatatg 720
 aggaagagat caaggctcct tccgacaagc tgaaggaggc tgagactcgg gctgagtttg 780
 cggagaggct agtaactaaa ttggagaaaa gcattgatga cttagaagac gagctgtacg 840
 ctcagaaaact gaagtacaaa gccatcagcg aggagctgga ccacgctctc aacgatatga 900
 cttccatata agtttctttg cttcacttct cccaagactc cctcgctcgag ctggatgtcc 960
 cacctctctg agctctgcat ttgtctattc tccagctgac cctggttctc tctcttagca 1020
 tcctgcctta gagccaggca cacactgtgc tttctattgt acagaagctc ttcgtttcag 1080
 tgtcaaataa acactgtgta agctaaaaaa a 1111

<210> 224
 <211> 284
 <212> PRT
 <213> Homo sapiens

<400> 224
 Met Asp Ala Ile Lys Lys Lys Met Gln Met Leu Lys Leu Asp Lys Glu
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 Asn Ala Leu Asp Arg Ala Glu Gln Ala Glu Ala Asp Lys Lys Ala Ala
 20 25 30
 Glu Asp Arg Ser Lys Gln Leu Glu Asp Glu Leu Val Ser Leu Gln Lys
 35 40 45
 Lys Leu Lys Gly Thr Glu Asp Glu Leu Asp Lys Tyr Ser Glu Ala Leu
 50 55 60
 Lys Asp Ala Gln Glu Lys Leu Glu Leu Ala Glu Lys Lys Ala Thr Asp
 65 70 75 80
 Ala Glu Ala Asp Val Ala Ser Leu Asn Arg Arg Ile Gln Leu Val Glu
 85 90 95
 Glu Glu Leu Asp Arg Ala Gln Glu Arg Leu Ala Thr Ala Leu Gln Lys

			100					105					110			
Leu	Glu	Glu	Ala	Glu	Lys	Ala	Ala	Asp	Glu	Ser	Glu	Arg	Gly	Met	Lys	
		115						120					125			
Val	Ile	Glu	Ser	Arg	Ala	Gln	Lys	Asp	Glu	Glu	Lys	Met	Glu	Ile	Gln	
	130					135						140				
Glu	Ile	Gln	Leu	Lys	Glu	Ala	Lys	His	Ile	Ala	Glu	Asp	Ala	Asp	Arg	
145				150				155							160	
Lys	Tyr	Glu	Glu	Val	Ala	Arg	Lys	Leu	Val	Ile	Ile	Glu	Ser	Asp	Leu	
			165					170						175		
Glu	Arg	Ala	Glu	Glu	Arg	Ala	Glu	Leu	Ser	Glu	Gly	Lys	Cys	Ala	Glu	
		180						185					190			
Leu	Glu	Glu	Glu	Leu	Lys	Thr	Val	Thr	Asn	Asn	Leu	Lys	Ser	Leu	Glu	
	195						200					205				
Ala	Gln	Ala	Glu	Lys	Tyr	Ser	Gln	Lys	Glu	Asp	Arg	Tyr	Glu	Glu	Glu	
210				215							220					
Ile	Lys	Val	Leu	Ser	Asp	Lys	Leu	Lys	Glu	Ala	Glu	Thr	Arg	Ala	Glu	
225				230						235					240	
Phe	Ala	Glu	Arg	Ser	Val	Thr	Lys	Leu	Glu	Lys	Ser	Ile	Asp	Asp	Leu	
			245					250						255		
Glu	Asp	Glu	Leu	Tyr	Ala	Gln	Lys	Leu	Lys	Tyr	Lys	Ala	Ile	Ser	Glu	
		260						265					270			
Glu	Leu	Asp	His	Ala	Leu	Asn	Asp	Met	Thr	Ser	Ile					
	275						280									

<210> 225
 <211> 501
 <212> DNA
 <213> Homo sapiens

<400> 225
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 aagatgggtga agcagatcga gagcaagact gcttttcagg aagccttgga cgctgcaggt 120
 gataaacttg tagtagttga cttctcagcc acgtgggtgtg ggccttgcaa aatgatcaac 180
 cctttctttc attccctctc tgaaaagtat tccaacgtga tattccttga agtagatgtg 240
 gatgactgtc aggatgttgc ttcagagtgt gaagtcaaat gcacgccaac attccagttt 300
 tttaagaagg gacaaaagggt ggggtgaattt tctggagcca ataaggaaaa gcttgaagcc 360
 accattaatg aattagtcta atcatgtttt ctgaaaacat aaccagccat tggctattta 420
 aacttgtatt tttttattta caaaatataa atatgaagac ataaccagtt gccatctgcg 480
 tgacaataaa cattatgcta a 501

<210> 226
 <211> 105
 <212> PRT
 <213> Homo sapiens

<400> 226
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 20 25 30
 Gly Pro Cys Lys Met Ile Asn Pro Phe Phe His Ser Leu Ser Glu Lys
 35 40 45
 Tyr Ser Asn Val Ile Phe Leu Glu Val Asp Val Asp Asp Cys Gln Asp
 50 55 60
 Val Ala Ser Glu Cys Glu Val Lys Cys Thr Pro Thr Phe Gln Phe Phe
 65 70 75 80
 Lys Lys Gly Gln Lys Val Gly Glu Phe Ser Gly Ala Asn Lys Glu Lys
 85 90 95

Leu Glu Ala Thr Ile Asn Glu Leu Val
 100 105

<210> 227
 <211> 783
 <212> DNA
 <213> Homo sapiens

<400> 227
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 cccagccgcc actagcgctc ccgccgcccg taaaggagct gagccgagcg ggggcgcccgc 120
 ccgggggtccg gtgggcaaaa ggctacagca ggagctgatg accctcatga tgtctggcga 180
 taaagggatt tctgccttcc ctgaatcaga caaccttttc aaatgggtag ggaccatcca 240
 tggagcagct ggaacagtat atgaagacct gaggtataag ctctcgctag agttccccag 300
 tggctaccct tacaatgcgc ccacagtga gttcctcacg ccctgctatc accccaacgt 360
 ggacacccag ggtaacatat gcctggacat cctgaaggaa aagtgggtctg ccctgtatga 420
 tgtcaggacc attctgctct ccatccagag ccttctagga gaacccaaca ttgatagtcc 480
 cttgaacaca catgctgccg agctctggaa aaaccccaca gcttttaaga agtacctgca 540
 agaaacctac tcaaagcagg tcaccagcca ggagccctga cccaggctgc ccagcctgtc 600
 cttgtgtcgt ctttttaatt tttccttaga tgggtctgtcc tttttgtgat ttctgtatag 660
 gactctttat cttgagctgt ggtatTTTTTg ttttgTTTTt gtctttttaa ttaagcctcg 720
 gttgagccct tgtatatata ataatgcat ttttgTcctt ttttaaaaaa aaaaaaaaaa 780
 aaa 783

<210> 228
 <211> 179
 <212> PRT
 <213> Homo sapiens

<400> 228
 Met Ala Ser Gln Asn Arg Asp Pro Ala Ala Thr Ser Val Ala Ala Ala
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 Arg Lys Gly Ala Glu Pro Ser Gly Gly Ala Ala Arg Gly Pro Val Gly
 20 25 30
 Lys Arg Leu Gln Gln Glu Leu Met Thr Leu Met Met Ser Gly Asp Lys
 35 40 45
 Gly Ile Ser Ala Phe Pro Glu Ser Asp Asn Leu Phe Lys Trp Val Gly
 50 55 60
 Thr Ile His Gly Ala Ala Gly Thr Val Tyr Glu Asp Leu Arg Tyr Lys
 65 70 75 80
 Leu Ser Leu Glu Phe Pro Ser Gly Tyr Pro Tyr Asn Ala Pro Thr Val
 85 90 95
 Lys Phe Leu Thr Pro Cys Tyr His Pro Asn Val Asp Thr Gln Gly Asn
 100 105 110
 Ile Cys Leu Asp Ile Leu Lys Glu Lys Trp Ser Ala Leu Tyr Asp Val
 115 120 125
 Arg Thr Ile Leu Leu Ser Ile Gln Ser Leu Leu Gly Glu Pro Asn Ile
 130 135 140
 Asp Ser Pro Leu Asn Thr His Ala Ala Glu Leu Trp Lys Asn Pro Thr
 145 150 155 160
 Ala Phe Lys Lys Tyr Leu Gln Glu Thr Tyr Ser Lys Gln Val Thr Ser
 165 170 175
 Gln Glu Pro

<210> 229
 <211> 777

<212> DNA

<213> Homo sapiens

<400> 229

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gaacatgtcc ggtctaagac caagggttcct gtgcaggacc aggttctttt gctgggctcc 180
aagatcttaa agccacggag aagcctctca tcttatggca ttgacaaaga gaagaccatc 240
caccttacc c tgaaagtggg gaagcccagt gatgaggagc tgcccttggt tcttgtggag 300
tcagggtgatg aggcaaagag gcacctcctc cagggtgcgaa ggtccagctc agtggcacia 360
gtgaaagcaa tgatcgagac taagacgggt ataatccctg agaccagat tgtgacttgc 420
aatggaaaga gactggaaga tgggaagatg atggcagatt acggcatcag aaagggcaac 480
ttactcttcc tggcatctta ttgtattgga ggggtgaccac cctggggatg ggggtgttggc 540
aggggtcaaa aagcttattt cttttaatct cttactcaac gaacacatct tctgatgatt 600
tcccaaaatt aatgagaatg agatgagtag agtaagattt ggggtgggatg ggtaggatga 660
agtatatgtc ccaactctat gtttctttga ttctaacaca attaattaag tgacatgatt 720
tttactaatg tattactgag actagtaa ataaatttttaa ggcaaaatag agcattc 777
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<210> 230

<211> 165

<212> PRT

<213> Homo sapiens

<400> 230

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Trp Asp Leu Met Thr Phe Asp Ala Asn Pro Tyr Asp Ser Val Lys Lys
20     25     30
Ile Lys Glu His Val Arg Ser Lys Thr Lys Val Pro Val Gln Asp Gln
35     40     45
Val Leu Leu Leu Gly Ser Lys Ile Leu Lys Pro Arg Arg Ser Leu Ser
50     55     60
Ser Tyr Gly Ile Asp Lys Glu Lys Thr Ile His Leu Thr Leu Lys Val
65     70     75     80
Val Lys Pro Ser Asp Glu Glu Leu Pro Leu Phe Leu Val Glu Ser Gly
85     90     95
Asp Glu Ala Lys Arg His Leu Leu Gln Val Arg Arg Ser Ser Ser Val
100    105    110
Ala Gln Val Lys Ala Met Ile Glu Thr Lys Thr Gly Ile Ile Pro Glu
115    120    125
Thr Gln Ile Val Thr Cys Asn Gly Lys Arg Leu Glu Asp Gly Lys Met
130    135    140
Met Ala Asp Tyr Gly Ile Arg Lys Gly Asn Leu Leu Phe Leu Ala Ser
145    150    155    160
Tyr Cys Ile Gly Gly
165
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<210> 231

<211> 4797

<212> DNA

<213> Homo sapiens

<400> 231

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ttctacaagc agtatccaag gggccgggtga tggttcaggga tgtttccata gacttctctc 180
aagaggaatg ggaatgcctg gacgctgatc agatgaattt atacaaagaa gtgatgttgg 240
agaatttcag caacctgggt tcagtgaggac tttccaattc taagccagct gtgatctcct 300
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tattggaaca	aggaaaagag	ccctggatgg	ttgatagaga	gctgactaga	ggcctgtggt	360
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aagtaataat	tacccgtgaa	gacatgtcta	cttttattca	gccacattt	cttattccac	480
ctcaaaaaac	tatgagtga	gagaaacat	gggaatgtaa	gatatgtgga	aagaccttta	540
atcaaaactc	acaatttatc	caacatcaga	gaattcattt	tgggtgaaaa	cactatgaat	600
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acactggtaa	aaaaccctat	gaatgtaagg	aatgtggcaa	ggcttttagt	tgtagtcat	720
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aacctccagc	tcctgagttc	aagcgattct	tgtgcctcag	cctctcaagt	agttgggatt	2100
acaygcagtc	gccaccatgc	ccggctaatt	tttttttttt	tttttttgta	tttttagtag	2160
cgacgggggt	tcaccatggt	ggccaggctg	gtcttgaact	cctgacttca	agtgatctgc	2220
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atccataaca	cagatactac	tagacctaag	aaaagagata	gacagcaata	caacaatagc	2460
aggggacttc	accactccat	tgacagcact	agacagatca	ctgggacaga	aatcaacaaa	2520
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ttctacccaa	caaccacaga	atatatactc	ttctcttctg	tgcattggaac	attctcaaaa	2640
ataggtcata	tactggacca	caaagcaagt	atcaataaat	tttaaaaaaa	caaaatcata	2700
tctaacatct	tctctgacca	tagtggata	aaactagata	tcaataccaa	gaggaactct	2760
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aactaagggtg	gaaattttaa	attttttgaa	ataaatgaaa	atagagacaa	aacacatgaa	2880
aacatctgag	atacagcaaa	agcagtgtta	agagaggatt	ttatagcatt	aaatgcctac	2940
acaaaaaaga	tagaaaaatc	tcaaataaat	agcctaactg	cacatctcaa	ggaactagga	3000
aaaaacaaaa	caaactcaac	ccaaagctgg	cagaagaaaa	gcaataacaa	atatcagagc	3060
aggcaaaaat	gagactgaga	acaaaggaat	gcaaaagatc	aataaaaaga	aaagttgggt	3120
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tattgaaatt	gaatcagtaa	tagaaaaaaa	tcttgcaaaa	acaaaaagcc	caggaccaga	3420
cagattcaca	gctgaattct	actagacatg	caaggaagaa	ctagtaacag	cactattgaa	3480
actattccaa	aaattatagg	agggaatcct	ccctaactca	ttctacaaag	ccagtatcat	3540
cctgatactg	aagccaggca	aggataaaac	acacaaaaaa	actacaagcc	aatatccctg	3600
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aaaaagatag	taacagcaca	gtcaagtgtga	ttttattcct	ggggtgtaag	gatggctcaa	3720
catatgcaac	tcaatacatg	attcatcaca	tacacagaat	taaaaataag	ccaggcactc	3780
acacctgtaa	tcccagcact	ttgcaaggcc	aaggcgggca	gatcacatga	tgtcaagagt	3840

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ttgagaccag tctggctgac atggcgaaac cctgtctcta ctaaaaatag aaaaattggc 3900
tgggcatggt ggcaggcact gtagtcccag ctacttggga ggctgaggca ggagaattac 3960
ttgaacctga gaagcggagg ttgcagtgag ctgagatagt gccattgcac tccagcctgg 4020
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aatcctattht agtacaaggt acattattta ggtaatgagt ccattaaaag ccaacacttt 4200
ccccactaca ctatatgtgt atgtaacaca actgcccttg taacttccta aacctataat 4260
taagaaacaa taaaaggcaa attaagaatg ctttttttaa aggtgggggc attatgctaa 4320
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tgggaacaga aaatgggtgt ataaattttt ttgacgtggg agtactggat attgtagaga 4440
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gttactataa actcttctgt ttctccatca cgttggtggg catctttact gattacaaat 4740
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<210> 232

<211> 433

<212> PRT

<213> Homo sapiens

<220>

<221> VARIANT

<222> 433

<223> Xaa = Any Amino Acid

<400> 232

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Glu Glu Glu Glu Arg Met His Asp Glu Leu Leu Gln Ala Val Ser Lys
20          25          30
Gly Pro Val Met Phe Arg Asp Val Ser Ile Asp Phe Ser Gln Glu Glu
35          40          45
Trp Glu Cys Leu Asp Ala Asp Gln Met Asn Leu Tyr Lys Glu Val Met
50          55          60
Leu Glu Asn Phe Ser Asn Leu Val Ser Val Gly Leu Ser Asn Ser Lys
65          70          75          80
Pro Ala Val Ile Ser Leu Leu Glu Gln Gly Lys Glu Pro Trp Met Val
85          90          95
Asp Arg Glu Leu Thr Arg Gly Leu Cys Ser Asp Leu Glu Ser Met Cys
100          105          110
Glu Thr Lys Ile Leu Ser Leu Lys Lys Arg His Phe Ser Gln Val Ile
115          120          125
Ile Thr Arg Glu Asp Met Ser Thr Phe Ile Gln Pro Thr Phe Leu Ile
130          135          140
Pro Pro Gln Lys Thr Met Ser Glu Glu Lys Pro Trp Glu Cys Lys Ile
145          150          155          160
Cys Gly Lys Thr Phe Asn Gln Asn Ser Gln Phe Ile Gln His Gln Arg
165          170          175
Ile His Phe Gly Glu Lys His Tyr Glu Ser Lys Glu Tyr Gly Lys Ser
180          185          190
Phe Ser Arg Gly Ser Leu Val Thr Arg His Gln Arg Ile His Thr Gly
195          200          205
Lys Lys Pro Tyr Glu Cys Lys Glu Cys Gly Lys Ala Phe Ser Cys Ser
210          215          220
Ser Tyr Phe Ser Gln His Gln Arg Ile His Thr Gly Glu Lys Pro Tyr
225          230          235          240
Glu Cys Lys Glu Cys Gly Lys Ala Phe Lys Tyr Cys Ser Asn Leu Asn

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290

				245					250					255			
Asp	His	Gln	Arg	Ile	His	Thr	Gly	Glu	Lys	Pro	Tyr	Glu	Cys	Lys	Val		
			260					265					270				
Cys	Gly	Lys	Ala	Phe	Thr	Lys	Ser	Ser	Gln	Leu	Phe	Leu	His	Leu	Arg		
		275					280					285					
Ile	His	Thr	Gly	Glu	Lys	Pro	Tyr	Glu	Cys	Lys	Glu	Cys	Gly	Lys	Ala		
	290					295					300						
Phe	Thr	Gln	His	Ser	Arg	Leu	Ile	Gln	His	Gln	Arg	Met	His	Thr	Gly		
305					310				315						320		
Glu	Lys	Pro	Tyr	Glu	Cys	Lys	Gln	Cys	Gly	Lys	Ala	Phe	Asn	Ser	Ala		
				325				330					335				
Ser	Thr	Leu	Thr	Asn	His	His	Arg	Ile	His	Ala	Gly	Glu	Lys	Leu	Tyr		
			340				345						350				
Glu	Cys	Glu	Glu	Cys	Arg	Lys	Ala	Phe	Ile	Gln	Ser	Ser	Glu	Leu	Ile		
	355					360					365						
Gln	His	Gln	Arg	Ile	His	Thr	Asp	Glu	Lys	Pro	Tyr	Glu	Cys	Asn	Glu		
	370					375					380						
Cys	Gly	Lys	Ala	Phe	Asn	Lys	Gly	Ser	Asn	Leu	Thr	Arg	His	Gln	Arg		
385					390				395						400		
Ile	His	Thr	Gly	Glu	Lys	Pro	Tyr	Asp	Cys	Lys	Glu	Cys	Gly	Lys	Ala		
			405					410					415				
Phe	Gly	Ser	Arg	Ser	Asp	Leu	Ile	Arg	His	Glu	Gly	Ile	His	Thr	Gly		
			420					425					430				

Xaa

<210> 233
 <211> 1860
 <212> DNA
 <213> Homo sapiens

<400> 233

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ccggctccgc	gcccttcccc	gagggctgga	tgatgggctg	tttcgccctg	caaacgggtg	180
acaccgagct	gaccgcggac	tcgggtggagt	ggtgcccgct	gcaaggctgc	aggcacctgc	240
tggcgtgcgg	gacctaccag	ctgcggcgcc	cggaggaccg	gcctgccggc	ccccagaaca	300
agggtggaat	ggaagttaag	gagcctcagg	tccgtttagg	ccgtctcttc	ctgtacagtt	360
tcaatgacaa	caactctatt	caccctcttg	tcgaggtcca	aagaaaagat	acttctgcaa	420
tcctggacat	gaaatggtgt	cacatcccgg	tggttggaac	tgccctcttg	ggcttggcag	480
atgccagtgg	atccatacaa	ctgctccggc	tggtggaatc	tgagaagagc	cacgtgctgg	540
agccattgtc	cagccttgcc	ctggaggagc	agtgtctggc	tttgtcccta	gattgggtcca	600
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ggcagctcca	cctcctgatg	gtgaatgaga	cgaggcccag	gctgcagaaa	gtggcctcat	720
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tgtattcagg	gggcgacgat	ggccttctga	ggggctggga	caccagggtg	cccggcaaatt	840
ttctcttcac	cagcaaaaaga	cacaccatgg	gtgtgtgcag	catccagagc	agccctcatc	900
gggagcacat	cctggccacg	ggaagctatg	atgaacacat	cctactgttg	gacacacgaa	960
acatgaagca	gccgttggca	gatacgccctg	tgaggggtgg	ggtatggaga	atcaagtggc	1020
accctttcca	ccaccacctg	ctcctggccg	cctgcattgca	cagtggcttt	aagatcctca	1080
actgccaaaa	ggcaatggag	gagaggcagg	aggcgacggg	cctgacatct	cacacattgc	1140
ccgactcgct	ggtgtatgga	gccgactggg	cctggctgct	cttccgttct	ctgcagcggg	1200
ccccctcgtg	gtcctttcct	agcaacctag	gaaccaagac	ggcagacctg	aagggtgcaa	1260
gcgagttgcc	aacaccctgt	catgaatgca	gagaggataa	cgatggggag	ggccatgcca	1320
gacccagag	tggaatgaag	ccactcacag	agggcatgag	gaagaatggc	acctggctgc	1380
aggctacagc	agccaccaca	cgtgactgtg	gcgtgaaccc	agaagaagca	gactcagcct	1440
tcagcctcct	ggccacctgc	tccttctatg	accatgcgct	ccacctctgg	gagtgggagg	1500
ggaactgagc	ttgaaatcat	gaagcccctt	cccacaagga	aaccaggagg	gagactgcga	1560


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gtgagtgcc  gggaccacct  catcagagat  gcttactgca  gccctgcagg  tgcctgggca  1620
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ctggggcccct  gaaagtggac  tgggtgattc  tgtctggcag  agagtgggga  aaagacgcgg  1740
tttccagctt  gcagatttgt  taagtttctc  aggcagattt  tgacttttcag  cctttcatac  1800
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<210> 234
<211> 501
<212> PRT
<213> Homo sapiens

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<400> 234
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Ser Ser Gly Arg Pro Arg Pro Arg Arg Pro Ala Gln Tyr Pro Ala Arg
          20          25          30
Pro Arg Arg Pro Ala Ser Thr Ala Gly Ser Ala Pro Phe Pro Glu Gly
          35          40          45
Trp Met Met Gly Cys Phe Ala Leu Gln Thr Val Asp Thr Glu Leu Thr
          50          55          60
Ala Asp Ser Val Glu Trp Cys Pro Leu Gln Gly Cys Arg His Leu Leu
65          70          75          80
Ala Cys Gly Thr Tyr Gln Leu Arg Arg Pro Glu Asp Arg Pro Ala Gly
          85          90          95
Pro Gln Asn Lys Gly Gly Met Glu Val Lys Glu Pro Gln Val Arg Leu
          100          105          110
Gly Arg Leu Phe Leu Tyr Ser Phe Asn Asp Asn Asn Ser Ile His Pro
          115          120          125
Leu Val Glu Val Gln Arg Lys Asp Thr Ser Ala Ile Leu Asp Met Lys
          130          135          140
Trp Cys His Ile Pro Val Ala Gly His Ala Leu Leu Gly Leu Ala Asp
145          150          155          160
Ala Ser Gly Ser Ile Gln Leu Leu Arg Leu Val Glu Ser Glu Lys Ser
          165          170          175
His Val Leu Glu Pro Leu Ser Ser Leu Ala Leu Glu Glu Gln Cys Leu
          180          185          190
Ala Leu Ser Leu Asp Trp Ser Thr Gly Lys Thr Gly Arg Ala Gly Asp
          195          200          205
Gln Pro Leu Lys Ile Ile Ser Ser Asp Ser Thr Gly Gln Leu His Leu
          210          215          220
Leu Met Val Asn Glu Thr Arg Pro Arg Leu Gln Lys Val Ala Ser Trp
225          230          235          240
Gln Ala His Gln Phe Glu Ala Trp Ile Ala Ala Phe Asn Tyr Trp His
          245          250          255
Pro Glu Ile Val Tyr Ser Gly Gly Asp Asp Gly Leu Leu Arg Gly Trp
          260          265          270
Asp Thr Arg Val Pro Gly Lys Phe Leu Phe Thr Ser Lys Arg His Thr
          275          280          285
Met Gly Val Cys Ser Ile Gln Ser Ser Pro His Arg Glu His Ile Leu
          290          295          300
Ala Thr Gly Ser Tyr Asp Glu His Ile Leu Leu Trp Asp Thr Arg Asn
305          310          315          320
Met Lys Gln Pro Leu Ala Asp Thr Pro Val Gln Gly Gly Val Trp Arg
          325          330          335
Ile Lys Trp His Pro Phe His His His Leu Leu Leu Ala Ala Cys Met
          340          345          350
His Ser Gly Phe Lys Ile Leu Asn Cys Gln Lys Ala Met Glu Glu Arg
          355          360          365

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Gln	Glu	Ala	Thr	Val	Leu	Thr	Ser	His	Thr	Leu	Pro	Asp	Ser	Leu	Val
370						375					380				
Tyr	Gly	Ala	Asp	Trp	Ser	Trp	Leu	Leu	Phe	Arg	Ser	Leu	Gln	Arg	Ala
385					390					395					400
Pro	Ser	Trp	Ser	Phe	Pro	Ser	Asn	Leu	Gly	Thr	Lys	Thr	Ala	Asp	Leu
				405	.				410					415	
Lys	Gly	Ala	Ser	Glu	Leu	Pro	Thr	Pro	Cys	His	Glu	Cys	Arg	Glu	Asp
			420					425					430		
Asn	Asp	Gly	Glu	Gly	His	Ala	Arg	Pro	Gln	Ser	Gly	Met	Lys	Pro	Leu
		435					440					445			
Thr	Glu	Gly	Met	Arg	Lys	Asn	Gly	Thr	Trp	Leu	Gln	Ala	Thr	Ala	Ala
	450					455					460				
Thr	Thr	Arg	Asp	Cys	Gly	Val	Asn	Pro	Glu	Glu	Ala	Asp	Ser	Ala	Phe
465					470					475					480
Ser	Leu	Leu	Ala	Thr	Cys	Ser	Phe	Tyr	Asp	His	Ala	Leu	His	Leu	Trp
				485					490					495	
Glu	Trp	Glu	Gly	Asn											
			500												

<210> 235
 <211> 1614
 <212> DNA
 <213> Homo sapiens

<400> 235

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ctcggttgcc	cggccgggga	cccgagccga	aaagttatcg	tcagaatgtc	gggcaaagac	180
cgaattgaaa	tctttccctc	gcgaatggca	cagaccatca	tgaaggctcg	tttaaaggga	240
gcacagacag	gtcgaaacct	cctgaagaaa	aaatctgatg	ccttaactct	tcgatttcga	300
cagatcctaa	agaagataat	agagactaaa	atgttgatgg	gcgaagtgat	gagagaagct	360
gccttttcac	tagctgaagc	caagttcaca	gcaggtgact	tcagcactac	agttatccaa	420
aatgtcaata	aagcgcaagt	gaagattcga	gcgaagaaag	ataatgtagc	aggtgttact	480
ttgccagtat	ttgaacatta	ccatgaagga	actgacagtt	atgaactgac	tggtttagcc	540
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gtggaactag	cttctctgca	gacttctttt	gttactttgg	atgaagctat	taagataacc	660
aacaggcgtg	taaatgccat	tgaacatgtc	atcattcccc	ggattgaacg	tactcttgct	720
tatatcatca	cagagctgga	tgagagagag	cgagaagagt	tctatagggt	aaagaaaata	780
caagagaaga	aaaagattct	aaaggaaaaa	tctgagaagg	acttggagca	aaggagagca	840
gctggagagg	tgttggagcc	tgctaattct	ctggctgaag	agaaggacga	ggatcttcta	900
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ttgtaaaatt	tacctagatg	tctattttatg	ggattacttt	tgcagaatca	taatttagca	1080
accatttatc	atggatgaaa	gagatctgta	aaacctgccc	aggaacttac	agaatttact	1140
ttgcagaagc	gttatcatac	tccattttaca	tctgtgttac	acgtgatctg	cttaccaagc	1200
atattaggaa	atacctctta	ggaagcatta	gcggtctcag	gccaattact	gtggagcagc	1260
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cctgtcttgt	ctgtcatggg	agccattctg	ccaattttaa	tgcgactgtg	gtataaacag	1440
taaaatgatt	taaaagtaag	tcattccggt	tttatttaatt	tactgttaag	tcattgttctc	1500
atgctcagat	cagtagtgtc	agccagagct	ttctctgcag	acatgtagga	agtgggtagc	1560
tatttttccc	actccatgta	ttagagtttt	acaaaaaggc	ttacttttga	gaca	1614

<210> 236
 <211> 247
 <212> PRT
 <213> Homo sapiens

<400> 236

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Met Ser Gly Lys Asp Arg Ile Glu Ile Phe Pro Ser Arg Met Ala Gln
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Thr Ile Met Lys Ala Arg Leu Lys Gly Ala Gln Thr Gly Arg Asn Leu
      20           25           30
Leu Lys Lys Lys Ser Asp Ala Leu Thr Leu Arg Phe Arg Gln Ile Leu
      35           40           45
Lys Lys Ile Ile Glu Thr Lys Met Leu Met Gly Glu Val Met Arg Glu
      50           55           60
Ala Ala Phe Ser Leu Ala Glu Ala Lys Phe Thr Ala Gly Asp Phe Ser
65           70           75           80
Thr Thr Val Ile Gln Asn Val Asn Lys Ala Gln Val Lys Ile Arg Ala
      85           90           95
Lys Lys Asp Asn Val Ala Gly Val Thr Leu Pro Val Phe Glu His Tyr
      100          105          110
His Glu Gly Thr Asp Ser Tyr Glu Leu Thr Gly Leu Ala Arg Gly Gly
      115          120          125
Glu Gln Leu Ala Lys Leu Lys Arg Asn Tyr Ala Lys Ala Val Glu Leu
      130          135          140
Leu Val Glu Leu Ala Ser Leu Gln Thr Ser Phe Val Thr Leu Asp Glu
145          150          155          160
Ala Ile Lys Ile Thr Asn Arg Arg Val Asn Ala Ile Glu His Val Ile
      165          170          175
Ile Pro Arg Ile Glu Arg Thr Leu Ala Tyr Ile Ile Thr Glu Leu Asp
      180          185          190
Glu Arg Glu Arg Glu Glu Phe Tyr Arg Leu Lys Lys Ile Gln Glu Lys
      195          200          205
Lys Lys Ile Leu Lys Glu Lys Ser Glu Lys Asp Leu Glu Gln Arg Arg
      210          215          220
Ala Ala Gly Glu Val Leu Glu Pro Ala Asn Leu Leu Ala Glu Glu Lys
225          230          235          240
Asp Glu Asp Leu Leu Phe Glu
      245

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<210> 237

<211> 1658

<212> DNA

<213> Homo sapiens

<400> 237

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gaactgccag ccaagatcct ggttgagttt gtggtggact ctcagaagaa agacaagctg 180
ctctgcagcc agcttcaggt agcggatttc ctgcagaaca tcctggctca ggaggacact 240
gctaagggtc tcgacccctt ggcttctgaa gacacgagcc gacagaaggc aattgcagct 300
aaggaacaat ggaaagagct gaaggccacc tacagggagc acgtagaggc catcaaaatt 360
ggcctcacca aggccctgac tcagatggag gaagcccaga ggaaacggac acaactccgg 420
gaagcctttg agcagctcca ggccaagaaa caaatggcca tggagaaacg cagagcagtc 480
cagaaccagt ggcagctaca acaggagaag catctgcagc atctggcgga ggtttctgca 540
gaggtgaggg agcgtaagac agggactcag caggagcttg acggggtgtt tcagaaactt 600
ggaaacctga agcagcaggc agaacaggag cgggacaagc tgcagaggta tcagaccttc 660
ctccagcttc tgtataccct gcagggtaag ctgttggtcc ctgaggctga ggctgaggca 720
gagaatcttc cagatgataa accccagcag ccgactcgac cccaggagca gagtacagga 780
gacaccatgg ggagagaccc tgggtgtgtc ttcaaggctg ttggtctaca acctgctgga 840
gatgtaaatt tgccatgact tcctggagga cagcagcatg gagaaagatc ctagaaaagg 900
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ctctctcagt tgtgtatttg ttcatcttca tatgctggca ggaacaacta ttaatacaga 1080

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tactcagaag ccaataacat gacaggagct gggactgggt tgaacacagg gtgtgcagat 1140
ggggaggggg tactggcctt gggcctccta tgatgcagac atgggtgaatt taattcaagg 1200
aggaggagaa tgtttttaggc aggtgggttat atgtgggaag ataattttat tcatggatcc 1260
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ctagtgatac cttgatcttt cccactttct gttttcggat tggagaagat gtaccttttt 1560
tgtcaactct tactttttatc agatgatcaa ctcacgtatt tggatcttta tttgttttct 1620
caaataaata tttaagggtta aaaaaaaaaa aaaaaaaa 1658

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<210> 238

<211> 277

<212> PRT

<213> Homo sapiens

<400> 238

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Met Glu Ala Ala Glu Thr Glu Ala Glu Ala Ala Ala Leu Glu Val Leu
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Ala Glu Val Ala Gly Ile Leu Glu Pro Val Gly Leu Gln Glu Glu Ala
 20          25          30
Glu Leu Pro Ala Lys Ile Leu Val Glu Phe Val Val Asp Ser Gln Lys
 35          40          45
Lys Asp Lys Leu Leu Cys Ser Gln Leu Gln Val Ala Asp Phe Leu Gln
 50          55          60
Asn Ile Leu Ala Gln Glu Asp Thr Ala Lys Gly Leu Asp Pro Leu Ala
 65          70          75          80
Ser Glu Asp Thr Ser Arg Gln Lys Ala Ile Ala Ala Lys Glu Gln Trp
 85          90          95
Lys Glu Leu Lys Ala Thr Tyr Arg Glu His Val Glu Ala Ile Lys Ile
100          105          110
Gly Leu Thr Lys Ala Leu Thr Gln Met Glu Glu Ala Gln Arg Lys Arg
115          120          125
Thr Gln Leu Arg Glu Ala Phe Glu Gln Leu Gln Ala Lys Lys Gln Met
130          135          140
Ala Met Glu Lys Arg Arg Ala Val Gln Asn Gln Trp Gln Leu Gln Gln
145          150          155          160
Glu Lys His Leu Gln His Leu Ala Glu Val Ser Ala Glu Val Arg Glu
165          170          175
Arg Lys Thr Gly Thr Gln Gln Glu Leu Asp Gly Val Phe Gln Lys Leu
180          185          190
Gly Asn Leu Lys Gln Gln Ala Glu Gln Glu Arg Asp Lys Leu Gln Arg
195          200          205
Tyr Gln Thr Phe Leu Gln Leu Leu Tyr Thr Leu Gln Gly Lys Leu Leu
210          215          220
Phe Pro Glu Ala Glu Ala Glu Ala Glu Asn Leu Pro Asp Asp Lys Pro
225          230          235          240
Gln Gln Pro Thr Arg Pro Gln Glu Gln Ser Thr Gly Asp Thr Met Gly
245          250          255
Arg Asp Pro Gly Val Ser Phe Lys Ala Val Gly Leu Gln Pro Ala Gly
260          265          270
Asp Val Asn Leu Pro
275

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